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HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN FOR CYCLIC ANHYDRIDES

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydrides Committee

Consortium Registration Number:

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MEMBER COMPANIES OF THE CYCLIC ANHYDRIDES COMMITTEE:

Buffalo Color Corporation

Dixie Chemical Company, Inc.

Lindau Chemicals, Inc.

Lonza Group
Lonza Inc./Lonza Spa

Milliken Chemical

CYCLIC ANHYDRIDE TEST PLAN

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INTRODUCTION

"Cyclic anhydrides" are being submitted as a category of chemicals under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge program by the Industrial Health Foundation Cyclic Anhydride Committee. Hereafter within this document, the term "cyclic anhydrides" will be used to denote only the anhydrides contained within this group.

Cyclic anhydrides are primarily "destructive industrial use" chemicals. They are not sold in consumer markets. Aside from occupational exposure, exposure of the general public would be limited to accidental release. Cyclic anhydrides are mainly used as curing agents (also called hardeners) in epoxy resin systems. The cured resins characteristically have high chemical resistance as well as good electrical insulation capacity and adhesive strength. Some of these chemicals are also used in the manufacture of alkyd and polyester resins.

As will be discussed in greater detail in the following test plan, anhydrides within the group have similar structure and physicochemical properties. Low molecular weight carboxylic acid anhydrides are also recognized to have similar toxicological properties. Of the more extensively studied anhydrides, phthalic anhydride is most structurally similar to the cyclic anhydrides. Within this report a toxicological analogy will be made to phthalic anhydride.

Available data indicates that the cyclic anhydrides have a low acute toxicity, are respiratory and skin sensitizers and can cause corrosive eye damage. Since these compounds are considered to be sensitizers at low concentrations, exposures in the workplace are controlled to lowest possible levels.

Relying on factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program, in which the use of chemical categories is encouraged, the IHF Cyclic Anhydride Committee concluded that hexahydrophthalic anhydride (CAS No.: 85-42-7), methyl-hexahydrophthalic anhydride (CAS No.: 25550-51-0; 5711-02-99), tetrahydrophthalic anhydride (CAS No.: 85-43-8), methyltetrahydrophthalic anhydride (CAS No.: 34090-76-1; 11070-44-3), and nadic methyl anhydride (CAS No.: 25134-21-8) constitute a "chemical category".

Two of the chemicals within the group, MHHPA and MTHPA are on the EPA's 1994 Inventory Update Rule (IUR) List of HPV Additions and are not formally included in the current HPV Challenge Program. One of the two chemicals, MTHPA has been sponsored by Hitachi Chemical Co. under the ICCA Program. As test data for MTHPA (CAS No.: 11070-44-3) is or will soon be available through the ICCA Testing Program, testing is not planned for MTHPA. MTHPA has been included in this submission due to chemical similarity.

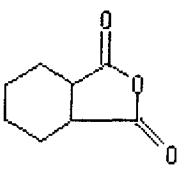
1. CATEGORY JUSTIFICATION

A. Structural Similarity

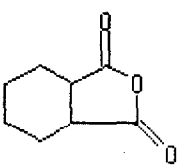
A key factor supporting grouping these chemicals in a single category is their structural similarity. All chemicals in this group contain a bicyclic ring structure with the carboxylic acid anhydride group as the single reactive and toxic functional moiety. This reactive moiety hydrolyses to form the diacid in water and is responsible for the irritant as well as sensitizing properties of the cyclic anhydrides. Two of the five bicyclic ring structures are saturated and three are partially unsaturated. One of the saturated and two of the partially unsaturated are substituted methyl derivatives. While the compounds with substituted methyl groups may exist as several isomeric forms (with different CAS numbers), there is no reason to believe this should affect the toxic potential of these compounds in any way.

Structures for chemicals within the chemical category are presented below.

- Hexahydrophthalic anhydride (CAS No.: 85-42-7), referred to in this report as HHPA

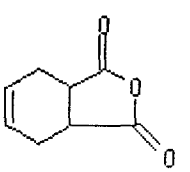


- Methylhexahydrophthalic anhydride (CAS No.: 25550-51-0)referred to in this report as MHHPA

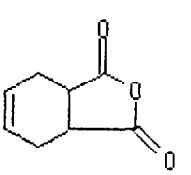


D1−Me

- Tetrahydrophthalic anhydride (CAS No.: 85-43-8), referred to in this report as THPA

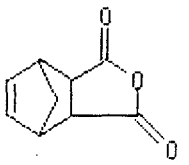


- Methyltetrahydrophthalic anhydride (CAS No.: 34090-76-1; 11070-44-3), referred to in this report as MTHPA



D1-Me

- Nadic methyl anhydride (CAS No.: 25134-21-8), referred to in this report as NMA.



D1–Me

Note: D1-Me indicates that for NMA, MTHPA, and MHHPA, the location of the methyl group may vary.

B. Chemical and Physical Similarity

The physicochemical properties of cyclic anhydrides suggest many general similarities. Molecular weight of anhydrides within the group varies from 152 to 178 classifying these compounds as low molecular weight (< 500) carboxylic acid anhydrides. All have relatively high boiling points and low vapor pressures indicating that vapor concentrations would be low under ambient conditions. All of the compounds will hydrolyze rather easily in water to produce the corresponding diacid. This indicates that solubility of the hydrolysis products and resultant pH is expected to be most relevant in the assessment of potential toxicity. Solubility data for the compounds themselves (which has been stated to be "low" or "negligible" on data sheets) is not of much value in the assessment of potential toxicological hazards. Aside from acidic pH resulting from hydrolysis to the diacid, other physical properties do not suggest a potential for environmental or toxicity concerns.

C. Toxicological Similarity

Review of existing published and unpublished test data for the cyclic anhydride category confirms similarity in toxicity. Workers exposed to cyclic anhydrides have occasionally developed conjunctivitis, skin sensitization, urticaria, rhinitis, occupational asthma, and an eczematous response. Respiratory sensitization is a major concern for all cyclic anhydrides.

All of the cyclic anhydrides that have been tested, as well as the closely related analogue phthalic anhydride (PA), have a low acute toxicity. Oral LD_{50}s for cyclic anhydrides in rats are relatively high, ranging from 958 to 4460 mg/kg. Dermal toxicity is also relatively low as indicated by dermal LD_{50}s of > 2000 mg/kg in rabbits for HHPA, MTHPA, and NMA. These values suggest a low order of acute oral and dermal toxicity. The four-hour inhalation $LC_{50}$for HHPA in rats is cited as > 1100 mg/m^3 (aerosol). In a limited inhalation study on NMA, a concentration of 750 mg/m^3 for 4 hours was lethal to 8 of 10 rats.

As demonstrated by animal testing and human experience, anhydrides within the group can cause mild to moderate skin irritation and moderate to severe eye irritation with possible corrosive effects. For European labeling purposes (Directive 67/548/EEC, Annex I) risk (R) phrases for HHPA, MHHPA, MTHPA, and THPA are: "Risk of serious damage to the eyes. May cause sensitization by inhalation and skin contact." Studies in rabbits indicate that NMA also causes severe eye irritation with the possibility of permanent damage. HHPA, MTHPA, THPA, and NMA all have caused mild skin irritation in rabbits. In one test, NMA was found to be moderately irritating and no studies were found indicating potential irritant effects MHHPA may have on the skin.

Similarities in toxicity of cyclic anhydrides has been recognized by the EPA's Office of Pollution Prevention and Toxics by designation of "anhydrides, carboxylic acid" as a valid chemical category for PMN review purposes. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers. Documentation for sensitization was available for all anhydrides within the group with the exception of NMA. Based on analogy to other acid anhydrides and verbal industrial reports, NMA is expected to produce sensitization.

Allergic response to cyclic anhydrides is triggered by the ability of cyclic anhydrides to bind covalently to free amino groups; in particular, to the amino group of lysine. An immunologic hapten-protein conjugate is formed which stimulates specific immunological responses. PA and cyclic anhydrides have been associated with occupational asthma.

Similarity in mechanism for allergic response to cyclic anhydrides within this group is also demonstrated by cross-sensitization potential. Workers sensitized to MTHPA, HHPA or HHPA/MHHPA have shown marked cross-reactivity to MTHPA-human serum albumin (HAS), HHPA-HAS, and MHHPA-HAS as demonstrated by radioallergosorbent test (RAST), RAST inhibition and skin prick tests. Ring structure, methyl group substituents and position of double bonds may all affect sensitizing potential of cyclic anhydrides; however differences are quantitative rather than qualitative.

2. PHYSICOCHEMICAL PROPERTIES

The majority of the physicochemical properties for the cyclic anhydrides were taken from various manufacturer's MSDSs and product specification sheets. In most cases, full documentation of the test value and underlying literature citation were unavailable. Due to this lack of documentation, testing or modeling is proposed for all values which are not in good agreement with each other as well as for values that appear to be taken from a single undocumented source. As MTHPA is currently sponsored under the ICCA Program, testing is not planned for this compound.

A. Melting Point

CAS No.	Melting Point	Reference	Year	Remarks
25134-21-8 NMA	< 18 °C	Buffalo Color Corp.	1995; 1997	None
85-42-7 HHPA	34-38 °C	Dixie Chemical Co., Inc.	1999	None
	35-36 °C	Hawley's Chemical Dictionary, 12th Ed.	1993	Glassy solid @ 35-36 °C.
	35-37 °C	Buffalo Color Corp.	1996	None
	37 °C	Lonza Inc./Lonza Spa	1995	None
85-43-8 THPA	99-101 °C	Hawley's Chemical Dictionary, 12th Ed.	1993	Solidification point.
	99 °C	Dixie Chemical Co., Inc.	1998	None
	100 °C	IUCLID Data Sheet	1994	None
	102 °C (minimum)	Lonza Inc/Lonza Spa	1995	None
34090-76-1 (11070-44-3) MTHPA	- 38 °C	Lonza Inc./Lonza Spa/ Hedset Data Sheet	1997/1995	Value is for mixture of 3- and 4-MTHPA. No decomposition or sublimation.
25550-51-0 MHHPA (5711-02-99)	- 30 °C	Lonza Inc./Lonza Spa	1995	None

Summary:
Values were obtained from manufacturer's MSDSs, product specification sheets, and a standard reference source. Melting point values for HHPA and THPA were taken from a standard reference source and are in agreement with those cited by the manufacturers. Limited data exists for the three remaining anhydrides – NMA, MTHPA, and MHHPA. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date cited is for the reference rather than date of test value determination.

Reliability:
[2] Valid with Restrictions (Klimisch)

Test recommendations: Testing is recommended for NMA to determine a specific value. Testing to determine the melting point for MTHPA and MHHPA is not recommended as these anhydrides have melting points well below 0 °C (OECD, Section 3.4 *Guidance for Meeting the SIDS Requirements*, Part 2.1, OECD Guideline 102).

B. Boiling Point

CAS No.	Boiling Point	Reference	Year	Remarks
25134-21-8 NMA	140 °C	Buffalo Color Corp.	1997	Approximate value @ 10 mm Hg.
	140 °C	Lonza Inc./Lonza Spa	1998	Approximate value @ 10 mm Hg.
85-42-7 HHPA	158 °C	Buffalo Color Corp.	1996	@ 17 mm Hg
	158 °C	Hawley's Chemical Dictionary, 12th Ed.	1993	@ 17 mm Hg
	144 °C	Dixie Chemical Co., Inc.	1999	@ 17 mm Hg
	296 °C	Lonza Inc./Lonza Spa	1995	@ 760 mm Hg.
	285 °C	Buffalo Color Corp.	1996	None
85-43-8 THPA	195 °C	Lonza Inc./Lonza Spa	1995	@ 50 mm Hg
	195 °C	IUCLID Data Sheet	1994	@ 1013 hPa. No decomposition.
34090-76-1 (11070-44-3) MTHPA	150 °C	HEDSET Data Sheet	1995	@ 13.5 hPa. No decomposition
	> 585 °F > 307.5°C	Lindau Chemicals, Inc.	1995	ASTM D-86
	283 °C	Dixie Chemical Co., Inc.	2000	@ 760 mm Hg
	290 °C	Lonza Inc./Lonza Spa	1996	@ 760 mm Hg
25550-51-0 (5711-02-99) MHHPA	290 °C	Lonza Inc./Lonza Spa	1995	None

Summary:

Values were obtained from manufacturer's MSDSs, product specification sheets, IUCLID document, and a standard reference source. The variance in boiling points for MTHPA are probably due to different mixtures of 3- and 4-MTHPA produced by the manufacturers. As MTHPA is currently sponsored under the ICCA, testing will not be proposed for this substance. The boiling point for HHPA was obtained from a standard reference source. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date cited reflects the reference year rather than the date of test value determination.

Reliability:
[2] Valid with Restrictions (Klimisch)

Test Recommendations:

Testing to obtain boiling point values using OECD Test Guideline 103 are recommended for THPA and MHHPA and NMA.

C. Vapor Pressure

CAS No.	Vapor Pressure	Reference	Year	Remarks
25134-21-8 NMA	0.1 mm Hg	Buffalo Color Corp.	Not Available	@ 20 °C
	1.5 mm Hg	Buffalo Color Corp.	Not Available	Estimated @ 30 °C
	5.0 mm Hg	Buffalo Color Corp.; Lonza Inc./Lonza Spa	1997; 1998	@ 120 °C.
85-42-7 HHPA	0.0068	Dixie Chemical Co., Inc.	1999	@ 25 °C
	0.25 mm Hg	Buffalo Color Corp.	1996	Calculated @ 30 °C
	5.0 mm Hg	Buffalo Color Corp.	Not Available	@ 106 °C
	10.0 mm Hg	Buffalo Color Corp.	1996	@ 125 °C
85-43-8 THPA	< 0.01 mm Hg	Dixie Chemical Co., Inc.	1998	@ 20 °C, calculated
	0.01 mm Hg	Lonza Inc./Lonza Spa	1995	@ 20 °C
	50.0 mm Hg	Dixie Chemical Co., Inc.	1998	@ 195 °C
34090-76-1 (11070-44-3) MTHPA	0.002 mm Hg	Dixie Chemical Co., Inc.	2000	@ 25 °C
	< 0.01 mm Hg	Lonza Inc./Lonza Spa	1995	@ 20 °C
	6.8 hPa	HEDSET Data Sheet	1995	@ 137 °C
	136 hPa	HEDSET Data Sheet	1995	@ 216 °C
25550-51-0 (5711-02-99) MHHPA	5.00 mm Hg	Lonza Inc./Lonza Spa	1995	@ 137 °C
	3.00 mm Hg	Dixie Chemical Co., Inc.	1999	@ 145 °C

Summary:

Values were obtained from manufacturer's MSDSs, product specification sheets, technical data sheets, and IUCLID documents. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date cited reflects the reference year rather than the date of test value determination. Values indicate that airborne vapor concentrations would be extremely low and aside from sensitization or respiratory irritation are unlikely to pose an acute or chronic inhalation hazard.

Reliability:

[2] Valid with Restrictions (Klimisch)

Test Recommendations:

As available data indicates low values, vapor pressures will be calculated for NMA, THPA, HHPA, and MHHPA. Vapor pressure vs temperature data will be calculated using PREDICT Version 4.09 software as supplied by Dragon Technologies, Inc. The method employed will be that of Pitzer (see Pitzer, K. S., et al, J. Am. Chem. Soc., 77, 3433 , 1955), using the following equation: Log $P_{VR} = P^{(0)} + \omega P^{(1)}$

Where P_{VR} is the vapor pressure at reduced temperature (temperature/critical temperature), $P^{(0)}$ and $P^{(1)}$ are tabulated functions (see reference) and ω is the accentric factor.

D. Partition Coefficient

CAS No.	Partition Coefficient (log Kow)	Reference	Year	Remarks
25134-21-8 NMA	1.35 ± 0.03	Buffalo Color Corp.	1997	Octanol/Water Partition Coefficient; Log_{10} Pow; P = 22.4
85-42-7 HHPA	1.33 ± 0.14	Buffalo Color Corp.	1996	Octanol/Water Partition Coefficient; Log_{10} Pow; P = 21.4
85-43-8 THPA	0.02	Hansch, L.	1989*	Calculated value from IUCLID data sheet.
34090-76-1 (11070-44-3) MTHPA	No Data			
25550-51-0 (5711-02-99) MHHPA	No Data			

Summary:

Values were calculated using OPPT's KOWWIN Model or taken from manufacturer's occupational and environmental health hazard summaries and IUCLID Documents. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. With the exception of the value for THPA, the date cited reflects the reference year rather than the date of test value determination.

Reliability:

[2] Valid with restrictions

Test Recommendations:

Octanol/water partition coefficients will be calculated for all of the cyclic anhydrides with the exception of MTHPA using EPISUITE Models.

E. Water Solubility

CAS No.	Water Solubility	Reference	Year	Remarks
25134-21-8 NMA	No Data			Hydrolyzes to diacid in water
85-42-7 HHPA	No Data			Hydrolyzes to diacid in water
85-43-8 THPA	10 g/L	IUCLID Data Sheet	1994	@ 20 °C. Slowly hydrolyzes to diacid in water.
34090-76-1 (11070-44-3) MTHPA	176.4 g/L	HEDSET Data Sheet	1995	@ 10 °C. Value may represent hydrolyzed product.
25550-51-0 (5711-02-99) MHHPA	36 g/L	HEDSET Data Sheet	1995	@ 20 °C. Value may represent hydrolyzed product.
	< 0.1%	Lonza Inc./Lonza Spa	1995	Hydrolyzes to diacid in water.

Summary:

Values were cited in manufacturer's MSDSs and IUCLID Documents. Cyclic anhydrides characteristically hydrolyze to form diacid in water. Solubility of the anhydrides is stated in various manufacturers' reference sources as low or negligible; however quantitative data is limited. High values are believed to reflect the solubility of the diacids following hydrolysis of the anhydride. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date cited reflects the reference year rather than the date of test value determination.

Reliability:

[4] Not assignable

Test Recommendations:

Water solubility testing for all members of the group with the exception of MTHPA in accordance with OECD Test Guideline 105 is proposed for all anhydrides in the group due to inadequacy of available data.

F. pH/pKa

CAS No.	pH/pKa	Reference	Year	Remarks
25134-21-8 NMA	pH = 2.4	FDRL Report 6771 F	1981	pH of 10% aqueous solution. By analogy to HHPA, pH of diacid was estimated at approximately 4
85-42-7 HHPA	pH = 4.2	FDRL Report	1981	Calculated value for 1% aqueous mixture.
85-43-8 THPA	pH = 2.1	IUCLID Data Sheet	1994	pH at 20 °C and 10 g/L.
34090-76-1 (11070-44-3) MTHPA	No Data			
25550-51-0 (5711-02-99) MHHPA	No Data			

Summary:

Values taken from manufacturer's MSDSs and IUCLID Documents. Characteristically anhydrides will hydrolyze to form the diacid in water. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date cited reflects the reference year rather than the date of test value determination.

Reliability:
[3] Not valid

Test Recommendations:

As these substances hydrolyze to form the diacid in water, testing for acids including dissociation constants (pKa) and conditions under which they were measured (OECD Guideline 112) will be conducted for all members of the group with the exception of MTHPA.

3. ENVIRONMENTAL FATE

Fate and Transport Characteristics

Limited environmental fate and distribution data is available for the five anhydrides. Due to the reactive nature of the carboxylic acid anhydride group, these chemicals are expected to hydrolyze in moist soils rather than adsorb to the soil. This conclusion is based on analogy to another closely-related cyclic anhydride, phthalic anhydride (PA). By analogy to PA, the cyclic anhydrides would not be expected to bioconcentrate in aquatic organisms, adsorb to sediments, or evaporate if released into water. Hydrolysis is expected to be a major fate process based on an estimated half-life for PA of 1.5 minutes. Release into the atmosphere is expected to result in direct photolysis via ring addition of photochemically produced hydroxyl radicals. The vapor-phase half-life of PA in the atmosphere is approximately 32 days. Limited photolysis data on HHPA suggests that it has an even shorter atmospheric half-life of about 7 days.

Biodegradation studies following OECD guidelines (i.e.: Method 301) have been conducted on four category members: HHPA, MHHPA, THPA, and NMA. Results showed no evidence of biodegradation potential for MHHPA and THPA as measured by BOD. NMA showed no biodegradation by BOD but did show a 1.0% biodegradation as measured by total organic carbon (TOC). HHPA also exhibited slight biodegradation potential (1.0-6%) as measured by BOD. All four cyclic anhydrides were hydrolyzed to their respective corresponding acids.

Due to limited environmental fate data available for members of the cyclic anhydride group, the IHF Cyclic Anhydride Committee proposes to complete environmental fate information for HHPA, MHHPA, THPA, and NMA by testing or modeling. As MTHPA is currently sponsored under the ICCA, testing is not proposed for this substance. The following tests are proposed:

NAME	ENDPOINT			
	PHOTODEGRADATION	HYDROLYSIS (stability in water)	TRANSPORT & DISTRIBUTION	BIODEGRADATION
HHPA	Data available [1]	OECD 111 (or estimation method)	Fugacity-based (EQC Level III)	Data available[2]
MHHPA	Calculation using EPISUITE Models	OECD 111 (or estimation method)	Fugacity-based (EQC Level III)	Data Available[2]
THPA	Calculation using EPISUITE Models	OECD 111 (or estimation method)	Fugacity-based (EQC Level III)	Data Available [2]
NMA	Calculation using EPISUITE Models	OECD 111 (or estimation method)	Fugacity-based (EQC Level III)	Data Available[2]

[1] Test data (computer modeling) is acceptable without restrictions (Klimisch Criteria = 1); however study-details were unavailable.
[2] Tests similar to OECD Method 301A have been conducted and appear adequate (Klimisch Criteria = 2).

4. ECOTOXICITY

Several fish, daphnia and algal studies were available in summary fashion for this category of compounds, but were not deemed adequate since only summary data and not full reports were available. This pertains to HHPA (two fish, one daphnia, and one algae studies), MHHPA (one fish study), THPA (one fish, one daphnia, one algae study), for the supporting compound MTHPA (one fish, one daphnia, and one algae studies), and no data for NMA. Three fish studies, one daphnia study, and one algae study were performed using OECD guidelines by the Japanese government, who made translated data summaries available; however, due to the lack of required data, the studies were deemed inadequate. Therefore, for this category, there are four compounds in the HPV program (HHPA, MHHPA, THPA, and NMA) and none of them have adequate fish, daphnia or algae data.

All of the category compounds are anhydrides and are believed or known to undergo substantial and relatively rapid hydrolysis. Hydrolysis will be measured for all four category compounds. Based on the results of that testing, if hydrolysis is not significant, the proposed testing will be on the parent material. If hydrolysis is significant, the proposed testing will be on the main hydrolysis byproduct, the diacids.

Using the model KOWWIN (part of the USEPA ECOSAR ecotoxicity modeling program), log octanol-water partition coefficients (log Kow) were calculated for the four category anhydride compounds. The log Kow values were 2.17 for HHPA, 2.59 for MHHPA, 1.96 for THPA, and 2.27 for NMA. These data support the decision to consider these four compounds as a single category. Therefore, it is proposed that ecotoxicity data for each compound will be generally similar across all compounds in the category. This would be true if all category compounds had similar stability in water (hydrolysis, see above). Assuming that testing shows that all four category compounds have similar stability in water, it is proposed that testing be conducted for two of the four compounds or corresponding diacids (as applicable) for fish, daphnia, and algae. If one or two compounds have different stability from the other compounds, fish, daphnia, and algae tests would be conducted with one of the parent materials (stable compounds).

5. TOXICITY

A. Acute

Acute oral mammalian toxicity data is available for all five anhydrides within the group. Some dermal and inhalation data were also available. Oral LD_{50}s in rats ranged from 958 to 4460 mg/kg reflecting a low order of acute oral toxicity. Dermal absorption toxicity was also low as indicated by dermal LD_{50}s of > 2000 mg/kg in rabbits for HHPA, MTHPA, and NMA. Oral toxicity data on a comparable anhydride (PA) showed LD_{50}s ranging from 800 to 4000 mg/kg in rats. Acute inhalation testing, available for two members of the group also indicates a relatively low order of acute toxicity. The four-hour LC_{50} for HHPA in rats is cited as > 1100 mg/m^3 (aerosol) which was the maximum attainable concentration under optimal conditions. In a limited study on NMA, a concentration of 750 mg/m^3 for 4 hours was lethal to 8 of 10 rats. It is important to note that respiratory sensitization is a major aspect of all cyclic anhydrides and probably occurs at exposure levels at or below 1 ppm. Any acute inhalation toxicity testing would most likely have to be conducted at concentrations of 1 to 2 orders of magnitude above those associated with respiratory sensitization. Since oral toxicity data are available for all five chemicals, dermal toxicity data are available for three chemicals in the group, and inhalation data is available for two members of the group, the IHF Committee believes that no additional acute toxicity testing is warranted. Available data is believed to be adequate to properly evaluate the cyclic anhydride group.

B. Repeated Dose

MTHPA, under the ICCA program, has been tested by oral gavage using OECD Method No. 422. Rats were dosed subchronically at 0, 30, 100 and 300 mg/kg/day. On terminal sacrifice, both male and female rats dosed at 300 mg/kg exhibited evidence of irritation at the site of administration, the forestomach. Less severe indications of irritation were evident in male rats at 100 mg/kg. No irritation was evident in males dosed at 30 mg/kg/day or females dosed at 30 mg/kg/day or 100 mg/kg/day. Aside from transient salivation in the animals dosed at 300 mg/kg/day, no adverse effects on body weight, food consumption, or other clinical signs were apparent. At termination, blood chemistry determinations indicated decreased total cholesterol and BUN as well as increased triglyceride level and adrenal weight in males. Aside from irritation at the site of administration, no specific target organ for MTHPA was elucidated. The NOELs were reported to be 30 mg/kg/day for males and 100 mg/kg/day for females. Other than the preceding subchronic data for MTHPA, adequate repeated-dose studies have not been conducted for the remaining cyclic anhydrides within this group.

Phthalic anhydride, a comparable analogue, has been the subject of an NCI lifetime oral bioassay in rats ($\leq$ 15,000 ppm in the diet) and mice (average dose: $\leq$ 32,692 ppm for males and $\leq$ 24,038 ppm for females in the diet). Under this chronic dosing regimen, there were decreased body weight gains at all doses but no adverse effect on survival. The lowest dietary dose of PA showing any histopathology in rats was 25,000 ppm in a range finding study. At this dose, the livers of rats (4 of 5 males) showed slight centrilobular cytoplasmic vacuolization. No histopathology was seen in mice at any dose level. PA was not carcinogenic in either species. Since data reflecting a low order of repeated exposure toxicity is available for one member of the category (MTHPA), and for a comparable analog (phthalic anhydride), repeated dose testing for one additional anhydride is expected to adequately characterize the subchronic toxicity potential within the proposed chemical category. The IHF Cyclic Anhydride Committee proposes to sponsor repeat dose testing for one category member, NMA. NMA will be tested in a 90-day oral toxicity study (OECD #408) in rats in conjunction with a one-generation reproductive study (OECD #415). NMA has been selected as the test compound on the basis of acute toxicity data suggesting that NMA is expected to be more toxic than other members of the group in repeat dose testing. If physicochemical, ecotoxicity, and environmental fate data for other members provide results which indicate these chemicals may differ significantly relative to mechanism of toxic action, then additional mammalian toxicity testing will be considered.

C. Genotoxicity (*in vitro* – Bacterial-Point mutation and Chromosomal aberration)

Using the standard Ames Test procedures as cited in OECD Test Guideline number 471, HHPA, THPA, and MTHPA were negative in *Salmonella typhimurium*, with and without metabolic activation. Phthalic anhydride, a closely-related analogue, also tested negative in the Ames Test with and without metabolic activation. At test concentrations that produced cytotoxicity and precipitate, PA induced an 18.5% increase in chromosomal aberrations (vs. 3% in controls) in Chinese Hamster Ovary (CHO) Cells without S9 activation and a small but non-significant increase in aberrations with S9 activation (Hilliard, 1998). Administration of PA at lower concentrations for a longer treatment period in an earlier CHO/chromosomal aberration (CA) study (Galloway, 1987) resulted in negative results with or without S9 activation. MTHPA results from this CHO/CA assay were negative for chromosomal aberration and equivocal for polyploidy.

Since gene mutation assays have been conducted on three of the five category members and *in vitro* chromosomal aberration studies have been conducted on MTHPA as well as the closely-related PA, additional testing for two chemicals will be conducted. The IHF Cyclic Anhydrides Committee proposes to conduct a chromosomal aberration assay (OECD Method 473) for HHPA and both a point mutation assay (Ames Test; OECD Method 471) and a chromosomal aberration assay (OECD Method 473) for NMA. Data from these assays combined with existing genotoxicity test data for MTHPA, THPA, HHPA, and PA are expected to provide sufficient data to adequately assess *in vitro* genotoxicity for the anhydrides as a category.

D. Reproductive/Developmental Toxicity

A combined screening study (OECD Method No. 422) was conducted to assess repeated dose toxicity, reproductive performance and developmental toxicity potential on MTHPA. Results from this study indicates that at doses less than or equal to 300 mg/kg/day, MTHPA had no adverse effects on reproductive performance in either male or female rats and no indications of developmental toxicity were evident. Limited studies on phthalic anhydride indicate the possibility of developmental and reproductive toxicity potential. Developmental effects were reported at doses of 59 mg/kg (5% incidence) and 203 mg/kg (50% incidence) in a screening study using 10 pregnant mice/dose dosed intraperitoneally on days 8-10 of gestation. No NOEL was reported (Fabro, 1982). Conversely, in a well-conducted feeding study, doses as high as 5% phthalic acid in the diet, (the diacid of phthalic anhydride) failed to produce developmental toxicity, even in the presence of maternal toxicity (Ema, 1997). The only study found relative to reproductive toxicity, was a limited USSR study (Protsenko, 1970). In this inhalation study, 6 male rats/level were exposed to 0, 0.02, 0.2 and 1 mg/m^3 phthalic anhydride, 24 hours/day for 45 days. The NOEL in this study was given as 0.02 mg/m^3. Sperm motility was slightly depressed at 0.2 mg/m^3 and significantly at 1 mg/m^3. No details were given concerning test compound purity, analytical sensitivity, compound generation, chamber measurements, etc., and the findings have never been reproduced.

To adequately characterize the cyclic anhydrides category, the IHF Cyclic Anhydrides Committee proposes to conduct an oral gavage one-generation reproduction study (OECD #415) in conjunction with a 90-day study on one of the category members, NMA (See Section B. above). The committee proposes these studies as opposed to conducting a screening study (OECD 422) which only provides limited information on chronic toxicity potential, reproductive performance and developmental toxicity potential.

The committee has proposed a traditional repeat dose test combined with a reproductive toxicity test instead of utilizing OECD Method 422 for several reasons. OECD Method 422 is a screening study that provides only limited information on chronic toxicity potential, reproductive performance and developmental toxicity potential. In general, the 54 day exposure period in OECD 422 is not expected to provide as much definitive evidence of systemic toxicity potential as a 90 day study. In the shorter exposure period, specific endpoints such as enzyme induction may or may not be detected. Due to limited data indicating that phthalic anhydride has a potential for male reproductive toxicity, the committee believes that a more definitive test is warranted. The 54-day test period used in OECD 422 is shorter than the complete male rat reproductive cycle of 65 days. To date, the only repeat dose/reproductive toxicity testing which has been conducted on category members has been the OECD 422 screening study for MTHPA. The Committee feels that definitive claims of no repeat dose and reproductive/ developmental toxicity cannot be made from data provided from OECD 422. The above considerations far outweigh the use of fewer animals per sex per group and cost savings, which appear to be the only advantages of the OECD 422 screening test. The committee believes that conducting a 90-day repeat dose and reproductive study will provide more detailed information for the five cyclic anhydrides. To date, no definitive subchronic study of adequate duration (for definition of target organs) has been located for any of the 5 cyclic anhydrides, including the comparison anhydride, phthalic anhydride.

If any suggestion of developmental toxicity (i.e.: malformations, implantation difficulties, etc.) is noted in the reproductive study, a developmental toxicity study (OECD #414) will be conducted on that material. Coupled with similar data on MTHPA from the ICCA Program, the preceding proposed studies on NMA are expected to provide sufficient data to characterize the cyclic anhydrides category relative to reproductive/developmental toxicity potential.

7. SUMMARY

The following tests and/or computer modeling are planned for the Cyclic Anhydride Category:

- HHPA (84-42-7): Vapor pressure; partition coefficient and water solubility/pKa; hydrolysis and transport/distribution; acute fish, acute Daphnia, and acute algae; *in vitro* point mutation and in *vitro* chromosomal aberration study

- MHHPA (25550-510-0): Vapor pressure; boiling point, partition coefficient, and water solubility/pKa; photodegradation, hydrolysis and transport/distribution

- THPA (85-43-8): Vapor pressure; boiling point, partition coefficient, and water solubility/pKa; photodegradation, hydrolysis and transport/distribution

- MTHPA (34090-76-1): Testing is not planned for this compound as MTHPA (11070-44-3) is currently sponsored under the ICCA program.

- NMA (255134-21-8): Vapor pressure; melting point, boiling point, partition coefficient and water solubility/pKa; photodegradation, hydrolysis and transport/distribution; acute fish, acute Daphnia and acute algae; 90-day oral toxicity study in conjunction with a one-generation reproduction study, *in vitro* point mutation and *in vitro* chromosomal aberration study
  Note: Additionally a developmental toxicity study will be conducted if developmental toxicity is suggested by the reproductive study.

As this test plan was developed, the IHF Cyclic Anhydride Committee considered the animal usage required and has, therefore, recommended only a minimal amount of animal testing – one combined 90-day toxicity study in conjunction with a one-generation reproduction study. By keeping the number of animals used in the proposed test plan to a minimum, the committee feels that animal welfare concerns have been properly addressed.

MATRIX OF APPLICABLE DATA ON CYCLIC ANHYDRIDE CATEGORY DATA AND PROPOSED TESTING						
TEST	**CATEGORY MEMBER; CAS NUMBER**					**REMARKS**
	HHPA; 85-42-7	**MHHPA; 25550-51-0 (5711-02-99)**	**THPA; 85-43-8**	**MTHPA; 34090-76-1 (11070-44-3)**	**NMA; 25134-21-8**	
PHYSICOCHEMICAL PROPERTIES						
Melting Point	A	A	A	(A)	T	
Boiling Point	A	T	T	(A)	T	
Vapor Pressure	T	T	T	(A)	T	
Partition Coefficient	T	T	T	(A)	T	
Water Solubility	T	T	T	(A)	T	Solubility and pKa testing will be done
ENVIRONMENTAL FATE						
Photodegradation	A	T	T	(A)	T	
Hydrolysis	T	T	T	(A)	T	
Transport and Distribution	T	T	T	(A)	T	
Biodegradation	A	A	A	(A)	A	
ECOTOXICITY						
Acute Fish	T	C	C	A	T	
Acute Daphnia	T	C	C	A	T	
Algae	T	C	C	A	T	
MAMMALIAN TOXICITY						
Acute Toxicity	A	A	A	A	A	
Repeated Dose	C	C	C	A	T	
Genotoxicity (*in vitro* – bacterial)	T	C	C	A	T	
Genotoxicity (*in vitro* – non-bacterial)	T	C	C	A	T	
Reproductive/Developmental Toxicity	C	C	C	A	T	

A – Endpoint requirement fulfilled with adequate existing data
C – Endpoint requirement fulfilled using Category Approach
T – Endpoint requirement to be fulfilled by testing or modeling.
(A) – Endpoint requirement to be fulfilled with data from ICCA Test Program.

AR201-13313B

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 1

ROBUST SUMMARIES

FOR

HEXAHYDROPHTHALIC ANHYDRIDE
(85-42-7)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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1. SUBSTANCE INFORMATION

CAS-Number 85-42-7

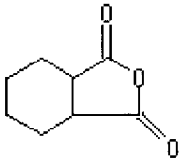
Name Hexahydrophthalic Anhydride

Name **1,3-Isobenzofurandione, Hexahydro-**

EINECS-Number 201-604-9

Molecular Formula $C_8H_{10}O_3$

Structural Formula



Other Chemical Identity/Synonyms 1,2-Cyclohexanedicarboxylic acid anhydride; Hexahydro-1,3-isobenzofurandione; Hexahydrophthalic acid anhydride; HHPAA

Molecular Weight 154.16

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [X]

Purity **99% weight/weight (approx.)**

SYNONYMS 1,3-Isobenzofurandione, Hexahydro; Cyclohexane-1,2-Dicarboxylic Anhydride; HHPAA

IMPURITIES

CAS No:	1687-30-5 (610-09-3, cis-; 2305-23-0 trans-)
EINECS No:	216-872-2
Name:	Hexahydrophthalic Acid
Value:	0.5% (maximum weight/weight)

Sulfated ash 0.1% max.; potassium 50 ppm max.; sodium 50 ppm max.; traces of tetrahydro PAA, hexahydrobenzoic acid and mixed anhydride
Reference: Buffalo Color Corp., 1/96

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

(a)

Value:	35-37 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

(b)

Value:	34-38 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

(c)

Value:	37 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, HHPA MSDS, 3/14/95

B. BOILING POINT

(a)

Value:	158 °C
Pressure:	17 mmHg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

(b)

Value:	144 °C
Pressure:	17 mmHg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

(c)

Value:	285 °C
Pressure:	No Data
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, 1/96

(d)

Value:	296 °C
Pressure:	760 mmHg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, HHPA MSDS, 03/14/95

C. VAPOR PRESSURE

(a)

Value:	5.00 mm Hg
Temperature:	106 °C
Method:	calculated [ ]; measured [ ]; ? [X] No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, Tech Data Sheet "Anhydrides"

(b)

Value:	10.00 mm Hg
Temperature:	125 °C
Method:	calculated [ ]; measured [ ] ? [X]
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

C. VAPOR PRESSURE

(c)

Value:	0.25 mm Hg
Temperature:	30 °C
Method:	calculated **[X]**; measured **[ ]** ? **[ ]**
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	Buffalo Color Corporation, 1/96

(d)

Value:	0.0068 mm Hg
Temperature:	25 °C
Method:	calculated **[X]**; measured **[ ]** ? **[ ]**
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

D. PARTITION COEFFICIENT $\log_{10}$Pow

Log_{10} Pow:	1.33 ± 0.14
Temperature:	No Data
Method:	calculated **[ ]**; measured **[ ]** ? **[X]**
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	Octanol/Water Partition Coefficient, P=21.4
Reference:	Fuhr, A.B./R.J. Dugan, 1982; Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

E. WATER SOLUBILITY

Value:	Insoluble - Hydrolyzes
Temperature:	No Data
Description:	Miscible**[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble [ ]; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[X]**
Method:	No Data
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	Hydrolyzes in water or dilute alkali to form diacid or salt. Slowly hydrolyzes in dilute acids. Miscible with benzene, toluene, acetone, carbon tetrachloride, and chloroform. Soluble in methanol.
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

F. pH VALUE, pKa VALUE

pH Value:	4.2
Concentration:	1% aqueous mixture
Temperature:	No Data
Method:	Calculated
GLP:	Yes [ ] No [ ] ? [X]
pKa value	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	FDRL Report, January 28, 1981

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

Type:	Air
Rate Constant:	0.45 X 10^{-11} cm^3/molecule/sec
Degradation:	50% after 7.2 days
Method:	Calculated. AOP Computer Programs, Vers. 1.53; Syracuse Research Center, 1994
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Half-life refers to 12-hour days
Reference:	IUCLID Data Sheet, 6/9/94. Atkinson, R., Atkinson, R., *A Structure-Activity Relationship for the Estimation of Rate Constants for the Gas-Phase Reactions of OH Radicals With Organic Compounds,* Int. J. Chem. Kinet 19:799-828, 1987.

B. STABILITY IN WATER

Type:	Field trial [ ]; Laboratory [ ]; Other [X]
Half life:	1 minute at 20 °C and pH=5.2
Degradation:	Not specified quantitatively
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	Hexahydrophthalic anhydride will hydrolyze to diacid upon contact with water.
Reference:	Buffalo Color Corporation, 1/96

C. BIODEGRADATION

(a)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Concentration:	10 mg/L related to DOC
Medium:	No Data
Degradation:	9.7% after – hours
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	No Data
Results:	Mean retention time of 3 hours
Test Conditions:	No Data
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[1] Valid without restrictions
Remarks:	None
Reference:	IUCLID Data Sheet, 6/9/94. Huels, *Unpublished Data*

(b)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Chemical concentration:	100 mg/L
Medium:	No Data
Degradation:	No Data
Kinetics:	No Data
Method:	*Method for Testing the Biodegradability of Chemical Substances by Microorganisms,* stipulated in *Testing Methods for New Chemical* Substances (July 13, 1974). Essentially the same test as in OECD Guidelines for Testing of Chemicals for Ready Biodegradability OECD Guideline 303A: Modified MITI Test (I) Guideline #301C, July 17, 1992.
Test Substance:	HHPA – 100% purity
Results:	Biodegradation (as measured by BOD) ranged from 1-6% at the end of the 28 day period in the three replicate tests. The percentage TOC ranged from 1-5% in the three test solutions at the end of the 28 day period. At the termination of cultivation, insoluble compound was not observed and sludge growth was not observed.
Test Conditions:	Concentration of test substance was 100 mg/L. Concentration of activated sludge was 30 mg/l (as the concentration of suspended solid). Volume of test solution was 300 ml. Cultivation temperature was 25 °C and cultivation duration was 38 days. Change in BOD was measured continuously. The pH of the test solutions (sludge and test substance) was adjusted to pH 7 initially and was pH 7 at the end of the cultivation period. The pH of the control vessel (test substance dissolved in water) was 3.9 at the end of the 28 day period.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reliability:	[1] Valid without restrictions
Remarks:	The percent biodegradation in the three test solutions as measured by BOD and TOC were as follows: Vessel 1 – 1% BOD, 5% TOC; Vessel 2 – 2% BOD, 1% TOC; and Vessel 3 – 6% BOD, 3% TOC. At the end of cultivation, insoluble compound and sludge growth were not observed in the test vessels. In the control solution, insoluble compound was not observed at the end of the 28 day period.
Reference:	Karume Laboratory, Chemicals Evaluation and Research Institute, Japan. *Unpublished Report*; May, 1985.

D. BOD_5,COD OR RATIO BOD_5/COD

ThOD:	1.87 g O_2/g
Method:	Calculated
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corp., 1/96

E. TRANSPORT AND DISTRIBUTION

No data.

4. ECOTOXICOLOGICAL DATA

A. ACUTE/PROLONGED TOXICITY TO FISH

Insufficient data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Insufficient data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Insufficient data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley rats
Value:	2700-2800 mg/kg (estimated, see Remarks)
Method:	5 rats/sex at doses of 1500, 2027, 2739, 3700 and 5000 mg/kg. Body weights were checked on days 1, 8 and 15. Daily observations and gross autopsies were conducted.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	25% TS (w/w) in corn oil slurry
Remarks:	Decreased activity and/or urinary incontinence were seen at all doses. Survivors had normal weight gains for 14 days post exposure. Mortality rates were 0 of 5 males and 1 of 5 females at 1500 mg/kg; 0 of 5 males and 0 of 5 females at 2027 mg/kg; 2 of 5 males and 3 of 5 females at 2739 mg/kg; 5 of 5 males and 4 of 5 females at 3700 mg/kg; and 5 of 5 males and 5 of 5 females at 5000 mg/kg. Necropsy was unremarkable in survivors. Decedents showed blood-like liquid, primarily in the intestines.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory, 1981.

(1) ACUTE ORAL TOXICITY (continued)

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	3307 mg/kg
Method:	No Data
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Remarks:	Moderately toxic. Limited data on doses and number of animals
Reliability:	[3] Not valid
Reference:	Oral report from Syracuse University Research Institute, 1980.

(2) ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley rats
Exposure time:	4 hours
Value:	LC_{50} > 1100 mg/m^3 (aerosol)
Method:	A group of five(5) male and five(5) female rats were exposed for 4 hours to an aerosol of an 80% (w/w) solution in ethanol – a maximum attainable concentration. Rats were observed daily. Body weights were taken on days 3, 4, 5, 8 and 15 post-exposure. Necropsies were done at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	80% (w/w) solution in ethanol
Remarks:	All rats survived and necropsies were unremarkable. Decreased activity was seen during exposure and body weights were depressed during the first week, followed by recovery in second week. Particle size was a geometric mean size of 5.8 μm (GSD = 2.2). Seventy-five (75) percent of the particles were less than 10 μm indicating a respirable aerosol.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory, Study No. 6771H, 1981.

(3) ACUTE DERMAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	New Zealand albino rabbits
Value:	LD_{50} > 2000 mg/kg
Method:	Limit test (OECD modification). Five male and five female rabbits were dosed with the solid material at 2000 mg/kg body weight on abraded skin, under a porous gauze dressing, for 24 hours and then observed for 14 days. Body weights were taken on days 1, 8 and 15 and gross autopsies were done at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Solid material – unknown purity
Remarks:	No rabbits died and no gross signs were seen except minimal irritation on day 2. Gross autopsy at termination was unremarkable.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory Study No. 6771 H, 1981.

B. REPEATED DOSE TOXICITY (General)

(a)

Species/strain:	Mice
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Intraperitoneal
Exposure period:	8 days
Frequency of treatment:	No Data
Post exp. observation period:	No Data
Dose:	500 mg/kg/day
Control group:	Yes [ ]; No [ ]; No Data [X]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	No Data
LOEL:	No Data
Results:	6 out of 6 "tumor bearing" mice survived 500 mg/kg x 8 days with no toxic signs reported.
Method:	No Data
GLP:	Yes [ ]; No [ ]; ? [X]
Test substance:	Comments: None
Reliability:	[3] Not valid
Reference:	Southern Research Laboratory Report NSC 8622 to CGNSC, 2/21/57.

(b)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Gavage
Exposure period:	300 days
Frequency of treatment:	5 days/week
Post exp. observation period:	No Data
Dose:	330 mg in olive oil/kg/day (10 animals/group)
Control group:	Yes [ ]; No [ ]; No Data [X]; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	No Data
LOEL:	No Data
Results:	5 out of 10 rats survived over 300 days at a feeding level of 330 mg/kg/day in olive oil. (2 killed by accident) No information on body weight, toxic signs or pathology.
Method:	No Data
GLP:	Yes [ ]; No [ ]; ? [X]
Test substance:	Comments: None
Reliability:	[3] Not valid.
Reference:	Letter: Ferber, K. H./B. M. Helfaer, 1957. Re: Syracuse U. Res. Inst. Oral Report, Item 5.0.21, 12/16/57.

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

Insufficient data.

(2) NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

Type:	Dermal Irritation/Corrosivity
Species/strain:	New Zealand albino rabbits
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating [ ]; Irritating **[ ]**; Moderate irritating [ ]; Slightly irritating **[X]**; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (caused burns) [ ]; Irritating **[X]**; Not irritating [ ]
Method:	Draize test. Application of 0.5 ml of various solutions to each of 6 rabbits with scoring at 24 and 72 hours.
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	Concentrations of 6.25, 12.5, 25, and 50% in mineral oil
Remarks:	Minimal to slight irritation was seen at $\leq$ 50%. Classified as "irritating" in accordance with EC Directive 6/548/EEC. Primary irritation scores were: 0.17 at 6.25%; 0.67 at 12.5%; 0.58 at 25%; and 0.92 at 50% (0.92 = minimal to slight irritation). Mineral oil alone scored 0.42.
Reliability:	[2] Valid with restrictions
Reference:	Food Drug Research Laboratory, Study No. 7232H, 1982.

(2) EYE IRRITATION/CORROSION

(a)

Type:	OECD (Irrigation and non-irrigation)
Species/strain:	New Zealand albino rabbits
Results:	Highly corrosive [ ]; Corrosive **[X]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating **[ ]**
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[X]**
Method:	Draize Test. One hundred (100) mg of solid material was applied to 6 rabbits without irrigation and to 3 rabbits each for irrigation at either 4 or 30 seconds. Irritant effects were scored up to 21 days.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Undiluted solid
Remarks:	HHPA may cause "Risk of Serious Damage to Eyes" in accordance with EC Directive 67/543/EEC. Unwashed eyes and those washed at 30 seconds showed severe irritation and corrosion with no recovery at 21 days. Rabbits irrigated at 4 seconds showed severe but reversible irritation by 19 days.
Reliability:	[2] Valid with restrictions.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

(b)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating [ ]; Irritating **[ ]**; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[X]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Draize Test
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	No Data
Reliability:	[3] Not valid
Remarks:	Washout after 4 seconds. Score of 39 on a Draize scale of 110 at 24 hours was reported.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

(c)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating [ ]; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[X]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Draize Test
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	Comments: None
Reliability:	[3] Not valid
Remarks:	Washout after 30 seconds. 86 on a Draize scale of 110 at 13 days.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

B. SKIN SENSITIZATION

Type:	
Species/strain:	Human
Results:	Sensitizing **[X]**; Not sensitizing **[ ]**; ambiguous [ ]
Classification:	Sensitizing **[X]**; Not sensitizing **[ ]**
Method:	No Data
GLP:	Yes **[X]** No [ ] ? **[ ]**
Test substance:	5% suspension HHPAA in mineral oil (10 repeat test). None
Reliability:	[2] Valid with restrictions
Remarks:	Four out of fifty-three subjects gave a low grade sensitivity reaction and one marked reaction indicating sensitization.
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96); FDRL Report of Study OE No. 2471, May 7, 1982.

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. All of the anhydrides within the cyclic anhydride category are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

Manufacturers of HHPA have not reported significant adverse effects on worker health but exposure levels are unknown. Transient effects (skin, eye, and respiratory tract irritation) have been noted as well as general signs like anemia, headache, fever and dizziness. Hypersensitivity effects have also been reported and include asthma, urticaria, contact dermatitis, fever, chills, hemolysis and respiratory sensitizations. Several key studies are subsequently summarized.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

(a)

Method:	A questionnaire, lung function, and blood tests were given to HHPA exposed workers to determine the presence of immunoglobulin-E(IgE) and immunoglobulin-G (IgG) antibodies against hexahydrophthalic human serum albumin (HHP-HSA). The 57 workers who reported symptoms or demonstrated specific antibodies were skin tested with HHP-HSA and interviewed and examined by a physician.
Results:	Sixteen of the 57 were found to have IgE mediated disease and seven had both IgE and IgG mediated disease.
Reliability:	[2] Valid with restrictions
Remarks:	IgE and IgG antibody status were found to be significant positive predictors for IgE and IgG disease respectively. The authors concluded that development of following exposure to HHPA, the development of immunologically mediated respiratory disease is most closely associated with development of IgE or IgG antibodies to HHP-HSA and exposure level. After the workers were removed from exposure for 1 year, no symptoms, physical findings, spirometry or chest x-rays indicated permanent damage due to HHPAA-induced respiratory disease; however, both serum IgE and IgG for HHPAA persisted in the workers after 1 year.
Reference:	Grammer, L.C., et al., 1994; Grammer, L. C., 1995

C. RESPIRATORY SENSITIZATION (continued)

(b)

Method:	Historical data
Results:	Source: Buffalo Color Corporation No serious incidents, case reports, or other epidemiology was noted in workers exposed to HHPAA.
Reliability:	[4] Not assignable
Remarks:	Manufactured by Buffalo Color Corporation for a number of years without reported significant adverse effects on health but early exposure levels are unknown. There have been cases of transient irritation.
Reference:	Buffalo Color Corporation, Occupational and Environmental Health Hazard Summary and Evaluation of Commercial Grade Chemicals, Issue No. 4, pg. 12, Date: 12/95.

(c)

Method:	In a cross-sectional study on 95 workers in two plants which used HHPA as a hardener for epoxy resin the radio allergo sorbent test (RAST) and enzyme linked immunosorbent assay were used to determine antibody levels to IgE and IgG respectively. The mean time of exposure was 7 hours (range 0.1-25) years.
Results:	The specific IgE and IgG levels were significantly increased in workers as compared with external referents or unexposed workers.
Reliability:	[2] Valid with restrictions
Remarks:	Study indicates that short-time peak exposures may affect IgE sensitization and HHPA can cause sensitization even at low levels.
Reference:	Welinder, H.E., et al., 1995.

(d)

Method:	Nasal challenge tests were performed with a conjugate of HHPA and human serum albumin (HAS) at three increasing concentrations in exposed workers to test the pathogenetic relevance of serum antibodies (IgE and IgG).
Results:	Eleven subjects who reported work-related nasal symptoms and were IgE-sensitized against HHPA (Positive in skin-prick test and RAST against HHPA-HAS conjugate) had a decrease of nasal inspiratory peak flow and a significant increase of symptoms after the challenges. Eleven unsensitized subjects with no symptoms and nine unsensitized subjects who complained of work-related nasal symptoms displayed no significant change in any parameter.
Reliability:	[2] Valid with restrictions
Remarks:	The authors concluded that symptoms in some of the workers were caused by an IgE-mediated mast cell degranulation and ensuing inflammatory reaction involving eosinophil and neutrophil cells.
Reference:	Neilsen, J., et al., 1994

(e)

Method:	Results from a radio allergo sorbent test (RAST) and skin prick test (using 1% and 5% acetonic solution) of commercially available phthalic anhydride were compared to results from RAST and skin prick tests using the not commercially available conjugates of HHPA and MTHPA. 110 employees exposed to HHPA and MTHPA were examined using the PA conjugates and 109 of the 110 were examined using HHPA and MTHPA conjugates.
Results:	Specific IgE against acid anhydrides was detected in a total of 17 persons and 6 sensitizations in the challenge test were clinically relevant. The PA conjugate RAST produced three false negatives and one false positive when compared with a RAST using HHPA and MTHPA conjugates when borderline positive findings using the PA conjugate RAST were included. In comparison with the RAST, the skin prick test gave three false positive and three false negative results.
Reliability:	[2] Valid with restrictions
Remarks:	The authors concluded that RASTs with conjugates of PA and skin prick tests with native acid anhydrides can validly ascertain workplace-related sensitizations to HHPA and MTHPA.
Reference:	Drexler, H., et al., 1994

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 2

ROBUST SUMMARIES

FOR

TETRAHYDROPHTHALIC ANHYDRIDE
(85-43-8)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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1. GENERAL INFORMATION

CAS-Number 85-43-8

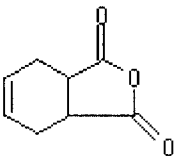
Name 4-Cyclohexene-1,2-dicarboxylic anhydride

CAS Descriptor Not Applicable

EINECS-Number 201-605-4

Molecular Formula $C_8H_8O_3$

Structural Formula



Other Chemical Identity/Synonyms 4-Cyclohexene-1,2-dicarboxylic acid, anhydride (cis); Tetrahydrophthalic anhydride; 1,2,3,6-Tetrahydrophthalic anhydride; THPA

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [X]

Purity >99% weight/weight (approx.)

SYNONYMS 4-Cyclohexene-1,2-dicarboxylic acid, anhydride (cis); THPA

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

(a)

Value:	99 °C (210 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, MSDS (8/13/98)

A. MELTING POINT (continued)

(b)

Value:	102 °C (216 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(c)

Value:	100 °C (212 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	EUCLID Data Sheet, 1994

B. BOILING POINT

(a)

Value:	195 °C
Pressure:	50 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(b)

Value:	195 °C
Pressure:	1013 hPa
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	EUCLID Data Sheet, 1994

C. VAPOR PRESSURE

(a)

Value:	<0.01 mm Hg
Temperature:	20 °C
Method:	calculated **[X]**; measured **[ ]**; ? **[ ]**
	No Data
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

(b)

Value:	0.01 mm Hg
Temperature:	20 °C
Method:	calculated **[ ]**; measured **[ ]**; ? **[X]**
	No Data
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(c)

Value:	50.0 mm Hg
Temperature:	195 °C
Method:	calculated **[ ]**; measured **[ ]**; ? **[X]**
	No Data
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

D. PARTITION COEFFICIENT $\log_{10}$Pow

Log_{10}Pow:	0.02
Temperature:	No Data
Method:	calculated **[X]**; measured **[ ]**; ? **[ ]**
GLP:	Yes **[ ]**; No **[ ]**; ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	EUCLID Data Sheet, 1994; Hansch, L. *Berechnung mit dem MedChem-Programm*, Version 1989 (POMONA89)

E. WATER SOLUBILITY

(a)

Value:	10 g/l
Temperature:	20 °C
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble **[X]**; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[3] Not valid
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	EUCLID Data Sheet, 1994; Huels, A.G., Sicherheitsdatenblatt, 10/1/93

(b)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble **[X]**
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[3] Not valid
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

(c)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble **[X]**; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	Slightly soluble with hydrolysis.
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

F. pH Value, pKa Value

(a)

pH Value:	2.1
Concentration:	1 g/l
Temperature:	20 °C
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
PKa Value:	No Data
Reliability:	[3] Not valid
Remarks:	No Data
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(b)

pH Value:	2.1
Concentration:	10 g/l
Temperature:	No Data
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
PKa Value:	No Data
Reliability:	[3] Not valid
Remarks:	No Data
Reference:	EUCLID Data Sheet, 1994; Huels, A.G., Sicherheitsdatenblatt, 10/1/93

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Remarks: Slowly hydrolyzes to diacid.

C. BIODEGRADATION

(a)

Type:	Aerobic [X]; Anerobic [ ]
Innoculum:	Activated sludge
Concentration:	100 mg/L (test substance)
Medium:	No Data
Degradation:	0.0%
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Tetrahydrophthalic anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD.
Test Conditions:	Three replicate tests were conducted. Concentration of the test substance was 100 mg/L. The activated sludge concentration was 30 mg/L. The volume of the test solution was 300 ml. A constant temperature of 25 °C was maintained for 28 days.
GLP:	Yes [X]; No [ ]; ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	Biochemical Oxygen Demand (BOD) was determined to calculate percent biodegradation.
Reference:	Report cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992.

C. BIODEGRADATION (continued)

(b)

Type:	Aerobic **[X]**; Anerobic [ ]
Innoculum:	Predominantly domestic sewage
Concentration:	10 mg/l related to DOC (Dissolved Organic Carbon)
Medium:	No Data
Degradation:	21% after 21 days
Kinetics:	No Data
Method:	OECD Guideline 301E, *Ready Biodegradability: Modified OECD Screening Test*
Test Substance:	'As prescribed by 1.1-1.4'
Results:	No Data
Test Conditions:	No Data
GLP:	Yes [ ]; No **[X]**; ? [ ]
Reliability:	[1] Valid without restrictions
Remarks:	None
Reference:	EUCLID Data Sheet, 1994; Huels-Untersuchung (unveroeffentlict), 1981

D. TRANSPORT AND DISTRIBUTION

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Insufficient data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Insufficient data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Insufficient data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} **[X]**; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	3 g/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Test substance:	No Data
Reliability:	[4] Not assignable
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol. 29(12):37, 1985

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	3300 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reliability:	[4] Not assignable
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol. 29(12):37, 1985

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Guinea Pig
Value:	3500 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reliability:	[3] Not valid
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol 29(12):37, 1985

(d)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	5410 mg/kg (4590-6380 mg/kg)
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	No details reported.
Reliability:	[4] Not assignable
Reference:	EUCLID Data Sheet, 1994; Marhold, J.V. Institut Prov Vychova Vedoucin Pracovniku Chemikeho Prymyelo Praha, p. 140, 1972

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

No Data

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

Insufficient data

(2) NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

(a)

Type:	Dermal Irritation/Corrosivity
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not Irritating [ ]
Method:	Draize test
GLP:	Yes [ ] No [ ] ? [X]
Test Substance:	No Data
Reliability:	[3] Not valid
Remarks:	500 mg was applied over a 24 hour time period.
Reference:	RTECS, 1999; Prehled Prumyslove Toxikologie, Organicke Latky, Masrhold, J., pg. 322, 1986.

(b)

Type:	Dermal Irritation/Corrosivity
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [X]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [ ]; Not Irritating [X]
Method:	Draize test.
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	'As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions
Remarks:	Irritation index: 0, 6/8 Redness: x=0,44 (EEC Annex VI) Edema: x=0
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1271, 1988 (unpublished)

(2) EYE IRRITATION/CORROSION

(a)

Type:	Acute Eye Irritation/Corrosion
Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[X]**; Highly Irritating [ ]; Irritating [ ]; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating [ ]; Not Irritating [ ]; Risk of serious damage to eyes **[X]**
Method:	OECD Guideline 405, *Acute Eye Irritation/Corrosion,* 1981
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test Substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No scores were calculated since only one animal used in the test. The test was stopped after one hour due to the possible risk of irreversible effects.
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1272, 1988 (unpublished)

(b)

Type:	Draize
Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating **[X]**; Slightly irritating **[ ]**; Not irritating [ ]
Classification:	Irritating **[X]**; Not Irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method:	Draize test
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test Substance:	No Data
Reliability:	[3] Not valid
Remarks:	Application of 20mg produced moderate irritation at 24 hours.
Reference:	RTECS, 1999; Prehled Prumyslove Toxikologie; Organicke Latky, Marhold, J., pg. 322, 1986

B. SKIN SENSITIZATION

Type:	Guinea Pig Maximization Test
Species/stain:	Guinea Pig
Results:	Sensitizing **[X]**; Not Sensitizing **[ ]**; ambiguous [ ]
Classification:	Sensitizing **[X]**; Not Sensitizing **[ ]**
Method:	OECD Guideline 406 *Skin Sensitization*, 1981
GLP:	Yes [ ] No **[X]** ? [ ]
Test Substance:	'As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions.
Remarks:	Seventeen (17) of the 20 guinea pigs showed a positive response.
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1218, 1988 (unpublished)

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

Method:	Guinea pigs were immunized intradermally with a single dose of 0.3 M solution of THPA and other anhydrides. Specific IgE and IgG antibodies specific for guinea-pig serum albumin conjugates of the anhydrides were determined by passive cutaneous anaphylaxis (PCA) tests and enzyme-linked immunoabsorbant assay (ELISA).
Results:	Specific IgG levels were increased in only three (3) of nine (9) animals immunized with THPA. Less than 10% of the animals in the THPA immunized group were positive for specific IgE antibodies.
Reliability:	[2] Valid with restrictions
Remarks:	Specific IgG, totals were analyzed by ELISA assay. PCA was used for analysis of IgE. It should be noted that the PCA assay has low sensitivity and may not detect low titer levels of antibody. Product purity was $\geq$ 97%. The primary purpose of this article was to investigate structure activity relationships of organic acid anhydrides. The authors concluded that substitution of a hydrogen atom for a methyl group enhanced antibody formation. This substitution appeared to be the most marked general effect of chemical structure on immunogenicity.
Reference:	Welinder, H., et al., 1995

7. REFERENCES

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 3

ROBUST SUMMARIES

FOR

METHYLHEXAHYDROPHTHALIC ANHYDRIDE
(25550-51-0)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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1 SUBSTANCE INFORMATION

CAS-Number 25550-51-0

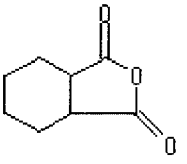
Name Methyl Hexahydrophthalic Anhydride

Name 1,3-Isobenzofurandione, Hexahydro-5-methyl-

EINECS-Number 247-094-1/243-072-0

Molecular Formula $C_9H_{12}O_3$

Structural Formula



D1—Me

Other Chemical Identity/Synonyms Hexahydromethyl-1,3-Isobenzofurandione; MHHPA; Hexahydromethyl- 1,2-Cyclohexane-dicarboxylic anhydride; 5-methyl hexahydro-1,3-isobenzofurandione; Hexahydro-4-Methylphthalic anhydride

Molecular Weight 168

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [ ]

Purity 99% weight/weight (approx.) – Lonza Group
>99% weight/weight (approx.) – Dixie Chemical Company

SYNONYMS

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

Value:	-30 °C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

B. BOILING POINT

(a)

Value:	290 °C
Pressure:	No Data
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

(b)

Value:	145 °C
Pressure:	3 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

C. VAPOUR PRESSURE

(a)

Value:	5.00 mm Hg
Temperature:	137 °C
Method:	calculated [ ]; measured [ ]; ? **[X]**
	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

(b)

Value:	3.00 mm Hg
Temperature:	145 °C
Method:	calculated [ ]; measured [X]; ? [ ]
	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

D. PARTITION COEFFICIENT $\log_{10}$Pow

No Data

E. WATER SOLUBILITY

(a)

Value:	<0.1% - Hydrolyzes
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Hydrolyzes in water.
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

(b)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[4] Not assignable
Remarks:	Reacts slowly with water.
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

(c)

Value:	36 g/L
Temperature:	20 °C
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	None
Reference:	HEDSET Data Sheet, 1995

F. **pH Value, pKa Value**

No Data

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Slowly hydrolyzes to diacid.

C. BIODEGRADATION

(a)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Concentration:	100 mg/L (test substance)
Medium:	No Data
Degradation:	0.0 %
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Methyhexahydrophthalic anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD. Three replicate tests were run. MHHPA was hydrolyzed to corresponding acid.
Test Conditions:	Test substance concentration was 100 mg/L. Activated sludge concentration was 30 mg/L with a test solution volume of 300 ml. Temperature was maintained at 25 °C and cultivation duration was 28 days.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Report summary cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992.

D. TRANSPORT AND DISTRIBUTION

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Insufficient Data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

No Data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

No Data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	3300 mg/kg
Method:	Oral ingestion.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No other data was supplied.
Reliability:	[2] Valid with restrictions
Reference:	Milliken Chemical Company, *Specialty Intermediates Pamphlet* AN-482-06 (9/96); Milliken Chemical Company, *Unpublished Report*, cited in MSDS No. 790773, January 17,2000.

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

No Data

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

No Data

(2) NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

No Data

(2) EYE IRRITATION/CORROSION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk (R) phrases for MHHPA include: "Risk of Serious Damage to the Eyes".

B. SKIN SENSITIZATION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk ® phrases for MHHPA include: "May cause sensitization by inhalation and skin contact."

C. RESPIRATORY SENSITIZATION

Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were found for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

(a)

Method:	Case report
Results:	This article includes a case report of a woman who worked as a cleaner in a condenser factory. The condensers were filled with epoxy resin, a hardener, an accelerator and pigment. Approximately seven months after MHHPA was brought into use as the hardener, the worker came down with rhinitis and coughing. RASTs and prick tests for MHHPA-HAS(Human Serum Albumin Conjugates) were positive. Bronchial challenge with MHHPA was negative but the intense rhinitis evoked by the test confirmed occupational IgE mediated allergic rhinitis due to MHHPA. Positive prick test reactions indicated cross-reactivity between MHHPA-HAS and PA, maleic anhydride, trimellitic anhydride and MTHPA. RASTs to PA and MTHPA were also positive.
Reliability:	[2] Valid with restrictions
Remarks:	Estimation or measurement of ambient air concentrations of MHHPA in the workplace were not given although occasional skin contact was noted.
Reference:	Kanerva, L., et al., 1991

(b)

Method:	Guinea pigs were immunized intradermally with a single dose of 0.3 M solution of MHHPA and other anhydrides. Specific IgE and IgG antibodies specific for guinea-pig serum albumin conjugates of the anhydrides were determined by passive cutaneous anaphylaxis (PCA) tests and enzyme-linked immunoabsorbant assay (ELISA).
Results:	Specific IgG levels were increased in all animals immunized with MHHPA and specific IgE antibodies were positive.
Reliability:	[2] Valid with restrictions
Remarks:	Product purity was $\geq$ 97%. Specific IgG, totals were analyzed by ELISA assay. PCA was used for analysis of IgE. The primary purpose of this article was to investigate structure activity relationships of organic acid anhydrides. The authors concluded that substitution of a hydrogen atom for a methyl group enhanced antibody formation. This substitution appeared to be the most marked general effect of chemical structure on immunogenicity.
Reference:	Welinder, H., et al., 1995

7. REFERENCES

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Grammer, L. C. et al., *Risk Factors for Immunologically Mediated Respiratory Disease from Hexahydrophthalic Anhydride*, J. Occup. Med. 36(6):642-646, 1994

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Kanerva, L. et al., *Airborne Allergic Contact Urticaria from Methylhexahydrophthalic Anhydride and Hexahydrophthalic Anhydride* Contact Dermatitis 41(6):339-341, 1999

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 4

ROBUST SUMMARIES

FOR

METHYLTETRAHYDROPHTHALIC ANHYDRIDE
(34090-76-1)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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1. SUBSTANCE INFORMATION

CAS-Number 34090-76-1

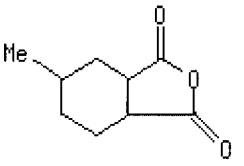
Name Methyltetrahydrophthalic Anhydride

Name Tetrahyro-5-methyl-1,3-Isobenzofurandione

EINECS-Number 251-823-9

Molecular Formula $C_9H_{10}O_3$

Structural Formula



Other Chemical Identity/Synonyms 4-Methyltetrahydrophthalic Anhydride; Tetrahydo-4-methylphthalic anhydride; MTHPA

Molecular Weight 166

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [X]; solid [ ]

Purity No Data

SYNONYMS Methyltetrahydrophthalic anhydride

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

No Data

B. BOILING POINT

(a)

Value:	> 585 °F
Pressure:	No Data
Decomposition:	No Data
Method:	ASTM D-86
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

(b)

Value:	283 °C
Pressure:	760 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

C. VAPOUR PRESSURE

(a)

Value:	0.002 mm Hg
Temperature:	25 °C
Method:	calculated **[X]**; measured [ ]; ? [ ]
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(b)

Value:	Negligible
Temperature:	16 ° C (60 ° F)
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

(c)

Value:	Negligible
Temperature:	60 °/100 ° F
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

D. PARTITION COEFFICIENT $log_{10}Pow$

No Data

E. WATER SOLUBILITY

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble **[X]**
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

F. pH Value, pKa Value

No Data

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Hydrolyzes to diacid.

C. BIODEGRADATION

No Data

D. TRANSPORT AND DISTRIBUTION

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Insufficient Data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Insufficient Data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Insufficient Data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [**X**]; LDL_0 [ ]; Other [ ]
Species/strain:	Crj:CD Rats
Value:	> 2000 mg/kg (for both males and females)
Method:	OECD Test Guideline 401
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Remarks:	Five (5) rats/sex were gavaged at 0, 500, 1000, or 2000 mg/kg of MTHPA in corn oil. Decreased birth weight, hypoactivity, shortness of breath and prone position were noted at 2000 mg/kg after 1 day. At necropsy, thickening, inflammation, adhesions, and squamous metaplasia of forestomach were seen at the two highest doses. No deaths occurred at any dose.
Reliability:	[1] valid without restrictions
Reference:	Safety Assessment Laboratory, Panapharm Laboratories Co., Ltc., 1285 Kurisaki-machi, Uto-shi, Kumamoto, 869-0, Japan, 1997.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [**X**]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley Derived Rats
Value:	3.69 ml/kg (~4.46 g/kg)
Method:	Groups of five male rats (205-275 g) were orally gavaged with undiluted material at dose levels of 0.464, 1.0, 2.15, 4.64 and 10 ml/kg. Animals were clinically observed for 14 days post-dosing. Gross autopsies were performed on all decedents and on all survivors at 14 days. This was an FHSA method (Code of Federal Regulations, Title 16, Chapter III, 1976).
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Undiluted liquid
Remarks:	The 95% confidence limits for this LD_{50} were 2.27-5.99 ml/kg. No deaths were seen at 0.464 or 1.0 ml/kg, 1 of 5 rats died at 2.15 ml/kg, 3 of 5 died at 4.64 ml/kg and 5 of 5 died at 10 ml/kg. At doses $\geq$ 2.15 ml/kg, clinical signs included hyperreactivity but no depression of bodyweight. Gross autopsy of decendents revealed gas and irritation in the intestinal tract and congestion of major organs. At 10 ml/kg, all deaths occurred within 24 hours. At other doses deaths occurred between 3 and 14 days. Gross autopsy on survivors was unremarkable.
Reliability:	[2] valid with restrictions
Reference:	Hill Top Research. *Unpublished Report* 78-645-21, July 25, 1978.

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [**X**]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	2140 µl/kg (~2589 mg/kg)
Method:	Range Finding Study
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Details not reported except for 95% confidence limit (1480-3100 ml/kg).
Reliability:	[2] valid with restrictions
Reference:	H. F. Smyth. American Industrial Hygiene Association Journal 30:470, 1969; Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} **[X]**; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit
Value:	1410 µl/kg (~1706 mg/kg)
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Details not reported
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969 Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(b)

Type:	LD_0 **[ ]**; LD_{100} [ ]; LD_{50} **[X]**; LDL_0 [ ]; Other **[ ]**
Species/strain:	Rat
Value:	>2000 mg/kg
Method:	Limit test; OCSE Linea Direttrice 402, 1987.
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	No Data
Remarks:	No details given.
Reliability:	[2] valid with restrictions
Reference:	Safephaun Laboratories Limited, U.K., 1987.

B. REPEATED DOSE TOXICITY (General)

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female **[ ]**; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1 dosc/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes [ ]; No **[ ]**; No Data [ ]; Concurrent no treatment [ ]; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:	Males – 30 mg/kg/day; Females – 100 mg/kg/day
LOEL:	Males – 100 mg/kg/day; Females – 300 mg/kg/day

Results:	MTHPA had no effect on body weight or food consumption at any dose level. The only adverse clinical sign was transient salivation in the 300 mg/kg groups. At termination, hematology was unremarkable in all groups but blood chemistry determinations showed decreased total cholesterol and BUN as well as increased triglycerides in males at 300 mg/kg. Upon autopsy, mucosal thickening of the forestomach in both sexes and increased adrenal weights in males were seen at the 300 mg/kg dose level. Histopathological examination revealed squamous metaplasia of the forestomach in males at 100 mg/kg and in both sexes at 300 mg/kg. Other forestomach changes seen at the 300 mg/kg dose included submucosal granulomatous inflammation, epithelial vacuolar change, edema, cellular infiltration and erosion. Other than suggestions of chronic irritation at the site of administration, no target organ for MTHPA was evident. The NOEL was reported to be 30 mg/kg in males and 100 mg/kg in females.
Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes **[X]**; No **[ ]**; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997.

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

Type:	Bacterial reverse mutation assay (Ames test)
Species/strain:	*Salmonella typhimurium* bacteria (Strains TA 98, TA 100, TA 1535, and TA 1537)); *Escherichia coli* bacteria (WP 2)
Test System:	Pre-incubation method
Concentration:	62.5-2000 µg/plate for *S. typhimurium* without S9 activation; 156-5000 µg/plate for *E coli* without S9 activation; 313-5000 µg/plate for *S. typhimurium* and *E. coli* with S9 activation
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Non-mutagenic
Cytotoxic Concentration:	500 µg/plate for TA 1535; 1000 µg/plate for TA 100, TA 98, and TA 1537 without S9 activation; 2500 µg/plate for *E. coli* without S9 activation; 5000 µg/plate for TA 100 and TA 1537 with S9 activation
Precipitation:	Not applicable
Genotoxic Effects:	Negative in *E. coli* and all strains of *S. typhimurium* with and without metabolic (S9) activation
Method:	OECD Guidelines 471 and 472
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity by weight)
Remarks:	Four strains of *S. typhimurium* (TA 98, TA 100, TA 1535, and TA 1537) and one strain of *E. coli* (WP2) were tested using a pre-incubation method. Three culture plates and two replicates were used at each dose level in both the presence and absence of a S9 rat liver homogenate. Appropriate positive controls were used with S9 (2AA) and without S9 (AF2, 9AA, SA) activation.
Reliability:	[1] Valid without restrictions.
Reference:	Hatano Research Institute Report, Food and Drug Safety Center, 729-5 Ochai, Hadano-shi, Kanagawa, 257, Japan, 1997.

(2) NON-BACTERIAL IN VITRO TEST (chromosome aberration)

Type:	Cytogenetic assay (chromosomal aberration)
Species/strain:	Chinese Hamster Lung (CHL/IU) cells
Test System:	Chinese Hamster Lung
Concentration:	Continuous treatment without S9 activation – 0, 0.075, 0.15, and 0.30 mg/ml; Short-term treatment without S9 activation – 0, 0.05, 0.10 and 0.20 mg/ml; Short-term treatment with S9 activation – 0, 0.11, 0.21, and 0.43 mg/ml.
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Negative for chromosomal aberration. Equivocal for polyploidy.
Cytotoxic Concentration:	Unknown
Precipitation:	Not applicable
Genotoxic Effects:	Structural chromosomal aberrations were not induced following 24 hours of continuous treatment. Polyploidy (1.13-1.88%) was weakly induced at 0.3 mg/ml without S9 activation after 48 hours of continuous treatment and at all concentrations (0.11-0.43 mg/ml) with short -term treatment and S9 activation.
Method:	OECD Guideline 473
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity by weight)
Remarks:	The maximum dose tested is a concentration of the test substance that produces a 50% or greater inhibition of cell growth or mitosis. Several lower graded dose levels were also used. Two culture plates/dose level were used and S-9 was prepared from rat liver induced with phenobarbital and 5,6-benzoflavone.
Reliability:	[1] Valid without restrictions.
Reference:	Hatano Research Institute Report, Food and Drug Safety Center, 729-5 Ochai, Hadano-shi, Kanagawa, 257, Japan, 1997.

D. REPRODUCTIVE TOXICITY

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No Data **[ ]**
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1 dose/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes **[ ]**; No **[ ]**; No Data **[ ]**; Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:	Males/Females – 300 mg/kg/day
LOEL:	Males/Females - > 300 mg/kg/day
Results:	No effects were observed on estrous cycle, numbers of corporeal lutea and implantations, copulation index, or fertility indices. Examination at delivery and during the lactation period showed no effects on the length of gestation, litter size, live newborns, gestational, stillborn and birth indices, sex ratio, body weight of offspring at birth and at day 4 after birth, or viability index on day 4. No external anomalies were apparent. The NOEL from this screening study was greater than 300 mg/kg for male and female reproductive performance and for developmental toxicity.

Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X]; No [ ]; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997

E. DEVELOPMENTAL TOXICITY

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female **[ ]**; Male [ ]; Male/Female [X]; No Data **[ ]**
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1dose/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes [ ]; No **[ ]**; No Data [ ]; Concurrent no treatment [ ]; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:	Males/Females – 300 mg/kg/day
LOEL:	No Data
Results:	No effects were observed on estrous cycle, numbers of corporeal lutea and implantations, copulation index, or fertility indices. Examination at delivery and during the lactation period showed no effects on the length of gestation, litter size, live newborns, gestational, stillborn and birth indices, sex ratio, body weight of offspring at birth and at day 4 after birth, or viability index on day 4. No external anomalies were apparent. The NOEL from this screening study was greater than 300 mg/kg for male and female reproductive performance and for developmental toxicity.
Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X]; No **[ ]**; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

Type of Test:	Primary Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [X]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method:	Draize test
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Score of 1 on a 10 point scale. Classified as irritating in accordance with EC Directive 67/548/EEC. No other details.
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969.

(2) EYE IRRITATION/CORROSION

Type of Test:	Primary Eye Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [X]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes [X]
Method:	Draize test
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Score of 9 on a 10 point scale. Classified as irritating in accordance with EC Directive 67/548/EEC.
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969.

B. SKIN SENSITIZATION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk ® phrases for MHHPA include: "May cause sensitization by inhalation and skin contact."

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

(a)

Method: A group of 145 workers exposed to MTHPA was investigated. The group was divided into three different exposure categories according to their contact with the epoxy resin. The average exposure levels at the time of the investigation were: 0.085 mg/m^3 (Zone I), 0.014 mg/m^3 (Zone II), and 0.010 mg/m^3 (Zone III) though the exposure was probably higher earlier.

Results: Specific IgE antibodies (RAST) to a conjugate between MTHPA and human serum albumin (HAS) were statistically significantly increased (P = 0.001; 26 subjects = 18% positive) in the exposed group, compared to a non-exposed control group (n = 33). Twenty-three exposed subjects were also skin-prick test positive to MTHPA-HAS. There was an association between exposure intensity and RAST-positive persons. The authors conclude that MTHPA is a sensitizing agent at low levels of exposure.

Reliability: [2] Valid with restrictions

Remarks: One worker positive to specific IgE antibodies to a conjugate between MTHPA and human serum albumin was only exposed for 2 months. Forty-four persons (30%) were smokers, and 16 (11%) atopics.

Reference: Welinder, et al., 1990

(b)

Method: In this case study, a 22 year old non-smoking male exhibited work-associated rhinitis and asthma. Bronchial hyperreactivity following provacation with methacholine, skin prick test positivity and specific immunoglobulin E (IgE) serum antibodies agains a MTHPA conjugate were noted.

Results: The disease appeared to be caused by an IgE-mediated allergy to MTHPA.

Reliability: [2] Valid with restrictions

Remarks: The patient had a heredity of rhinitis. About 4 months after beginning a job which involved working with MTHPA and methyl imidazole, he experienced nasal secretion and congestion during work. Some time later, he developed chest tightness, a continual productive cough and occasional wheezing. A skin prick test was positive to a conjugate of MTHPA and human serum albumin (HAS). None of the 34 unexposed reference workers in a nearby factory were positive to MTHPOA-HAS. The total immunoglobulin (Ig)E level was 235 kU/I. In the radioallergosorbent test (RAST), specific IgE antibodies to MTHPA-HAS were found (RAST ratio 7.5). In the enzyme-linked immunosorbent assay (ELISA), specific IgG antibodies were not present (optical density 0.32). Sera from 30 referents had a median total IgE of 11 (range 1-127) kU/I. When tested with MTHPA-HAS, the referents' RAST ratio for IgE was 1.1 (range 0.7-2.0), and their ELISA value for specific IgG was 0.04 (range 0-0.4) in optical density. After a period of vacation, he was removed from exposure to MTHPA. Symptoms gradually disappeared during the next five weeks. The day before a second examination, he was once more exposed to MTHPA at his work site. After about 2 H of exposure, he suffered from nasal congestion and irritation. The time weighted MTHPA exposure at the original job site was 0.1 mg/m^3.

Reference: Nielsen, J., et al., 1989

(c)

Method: In this case study, a patient positive to a prick test with MTHPA-HAS and specific IgE determination (who had been occupationally exposed to MTHPA) underwent a bronchial provocation test to cold MTHPA, heated MTHPA, and a placebo.

Reliability: [2] Valid with restrictions

Results: The bronchial provocation test with the placebo and cold MTHPA (0.2 mg/m^3) were negative. The bronchial provocation test to MTHPA heated to workroom temperature (100 °C) was positive. The MTHPA concentration in the chamber air was 7 mg/m^3 during the 30 minute provocation test. Wheezing and rales were induced after 6 H. After six months without exposure, the patient had fewer symptoms. The patient was diagnosed with probable occupational asthma caused from sensitization to MTHPA.

Reference: Kanerva, L., et al., 1991

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 5

ROBUST SUMMARIES

FOR

NADIC METHYL ANHYDRIDE
(25134-21-8)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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1. SUBSTANCE INFORMATION

CAS-Number 25134-21-8

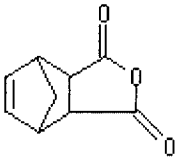
Name Nadic Methyl Anhydride

Name 5-Norbornene-2,3-Dicarboxylic Anhydride, Methyl-; Methyl-5-norbornene-2,3-dicarboxylic; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a-tetrahydromethyl; Methylbicyclo (2,2,1) hept-5-ene-2,3-dicarboxylic anhydride; Nadic Methyl Anhydride; NMA

EINECS-Number 2466448

Molecular Formula $C_{10}H_{10}O_3$

Structural Formula



D1—Me

Other Chemical Identity/Synonyms Methyl-5-norbornene-2,3-dicarboxylic anhydride; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a -tetrahydromethyl; Methylbicyclo (2,2,1) hept-5-ene-2,3-dicarboxylic anhydride; Nadic Methyl Anhydride; NMA

Molecular Weight 178.2

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [X]; solid [ ]

Purity 99% weight/weight

SYNONYMS Bicyclo (2,2,1) Hept-5-ene-2,3-Dicarboxylic Anhydride, Methyl; 5-Norbornene-2,3-Dicarboxylic Anhydride,Methyl-; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a-tetrahydromethyl; Nadic Methyl Anhydride; NMA

IMPURITIES

CAS No:	Not Found
EINECS No:	Not Listed
Name:	Free Acid
Value:	1% (maximum weight/weight)

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

Value:	<18 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Becomes "glassy"
Reference:	Buffalo Color Corporation, 12/95; Buffalo Color Corporation, *MSDS 127-2641* (12/8/97)

B. BOILING POINT

Value:	140 °C (Approximate)
Pressure:	10 mm Hg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2641 (12/8/97); Lonza Inc./Lonza Spa, NMA MSDS, 12/14/98

C. VAPOR PRESSURE

(a)

Value:	1.5 mm Hg
Temperature:	30 °C
Method:	calculated [ ]; measured [ ] ? [X] No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Estimated
Reference:	Buffalo Color Corporation, Technical Bulletin, "Anhydrides"

(b)

Value:	5.0 mm Hg
Temperature:	120 °C
Method:	calculated [ ]; measured [ ] ? [X] No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2641 (12/8/97); Lonza Inc./Lonza Spa, NMA MSDS, 12/14/98

(c)

Value:	0.1 mm Hg
Temperature:	20 °C
Method:	calculated [ ]; measured [ ] ? [X]
	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Approximate
Reference:	Buffalo Color Corporation, Technical Bulletin, "Anhydrides"

D. PARTITION COEFFICIENT log_{10}Pow

Log_{10} Pow:	1.35 ± 0.03
Temperature:	No Data
Method:	calculated [ ]; measured [ ] ? [X]
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Octanol/Water Partition Coefficient, P = 22.4
Reference:	Fuhr, A.B./J.A. Gouck, 1980 (memo); Buffalo Color Corporation, MSDS 127-2641 (12/8/97)

E. WATER SOLUBILITY

Value:	Insoluble
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [X]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Insoluble in water, but will hydrolyze to diacid in presence of water or and cold acid (pH = 5). Hydrolyzes and forms dibasic salt in cold alkalis (pH=9). Soluble in toluene, acetone, benzene, naptha, and xylene. Probably soluble in $CHCl_3$, 1,1,1-Trichloroethylene, ether and cyclohexane.
Reference:	Buffalo Color Corporation, 12/95; Buffalo Color Corporation, MSDS 127-2641 (12/8/97)

F. pH Value, pKa Value

pH Value:	2.4
Concentration:	10% aqueous solution
Temperature:	No Data
Method:	No Data
GLP:	Yes [X] No [ ] ? [ ]
pKa value	Not Given
Reliability:	[4] Not assignable
Remarks:	pH of diacid estimated at approximately 4 by analogy to HHPAA
Reference:	FDRL Report of Study 6771F, February 27, 1981.

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Not Stable – Will hydrolyze to diacid.

C. BIODEGRADATION

(a)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Concentration:	10 mg/L (test substance)
Medium:	No Data
Degradation:	0.0 %
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Nadic methyl anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD. Approximately 1.0% biodegradation as measured by TOC. NMA was hydrolyzed to the corresponding acid in the three replicate tests conducted.
Test Conditions:	The test substance concentration was 100 mg/L. The activated sludge concentration as the concentration of suspended solid was 30 mg/L. The volume of the test solution was 300 ml. Cultivation temperature was constant at 25 °C for the 28 day duration.
GLP:	Yes [X] No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	Biochemical Oxygen Demand (BOD) was determined and Total Organic Carbon (TOC) was analyzed.
Reference:	Report summary cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992

(b)

Type:	Calculated ThOD
Value:	ThOD = 1.89 g O_2/g
Method:	No Data – Calculated.
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Buffalo Color Corp., 12/95

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

No Data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

No Data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

No Data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley Rats - Female and Male
Value:	958 mg/kg (856-1077 CL)
Method:	Single undiluted oral dose was administered to 5 rats/sex/dose at doses of 650, 801, 987, 1217 and 1530 mg/kg. OECD Study.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Undiluted liquid
Reliability:	[1] Valid without restrictions.
Remarks:	Mortality occurred at all dose levels: One (1) of 5 males and 0 of 5 females at 650 mg/kg; 1 of 5 males and 1 of 5 females at 801 mg/kg; 2 of 5 males and 2 of 5 females at 987 mg/kg; 5 of 5 males and 4 of 5 females at 1217 mg/kg; 5 of 5 males and 5 of 5 females at 1530 mg/kg. All deaths occurred within 6 days post-dosing. Clinical signs in those rats that died included weight loss, blood in urine, and decreased activity. Survivors gained weight normally. Necropsy findings in decedents included dark lungs and blood-like fluid in the intestines.
Reference:	Food and Drug Research Laboratories, Study No. 6771F, 1/20/81.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	914 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test Substance:	No Data
Reliability:	[4] Not assignable
Remarks:	Limited data available. Details of toxic effects not reported.
Reference:	NIOSH/RTECS, April 1989, RB 91000

(2) ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [X]
Species/strain:	Sprague-Dawley Rats – Female and Male
Exposure time:	4 hours
Value:	750 mg/m^3 (aerosol), lethal level
Method:	Modified OECD Limit Test. Five(5) rats/sex were exposed to an aerosol of NMA for 4 hours and observed for 14 days. Toxic signs and body weights were taken periodically and gross autopsies were conducted at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	90% NMA in ethyl alcohol
Reliability:	[2] valid with restrictions.

Remarks: Aerosol concentration was determined gravimetrically. Geometric mean particle size was 3.2 μm with a GSD of 2.1. Ninety-three percent (93%) of particles were less than 10 μm. Three (3) of five males and 5 of 5 females died between 3 and 7 days post-dosing. Toxic signs included labored breathing, nasal discharge, urinary incontinence and bloody urine, cloudy eyes and weight loss. Gross autopsy showed pale organs related to vascular congestion. A parallel study with an ethyl alcohol aerosol produced no effects.

Reference: Food and Drug Research Laboratories, Study No. 6771F, 3/24/81.

(3) ACUTE DERMAL TOXICITY

(a)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Ti_FRAI_f rats

Value: 4920 mg/kg (3670-6590 CL)

Method: NMA was applied dermally at doses of 2000, 3000, 4000 and 5000 mg/kg for 24 hours and rats were observed for 14 days post-dosing. Five (5) males and 5 females were used at each dose. Clinical signs and body weights were periodically monitored. At termination of dosing, at 24 hours and periodically thereafter, the skin was carefully examined for adverse reactions.

GLP: Yes [ ] No [ ] ? [X]

Test substance: No Data

Reliability: [2] valid with restrictions.

Remarks: Mortality was: 0 of 5 M and 0 of 5 F at 2000 mg/kg; 1 of 5 M and 1 of 5 F at 3000 mg/kg; 2 of 5 M and 1 of 5 F at 4000 mg/kg; and 2 of 5 M and 3 of 5 F at 5000 mg/kg. Clinical signs included a reduction in spontaneous motility, ataxia, eyelid closure, dulled response to pain, and irregular respiration (disappeared in survivors by 5 days post-dosing). On the basis of skin reactions, the authors called NMA a mild skin irritant.

Reference: CIBA-Geigy Laboratory, 9/27/77.

(b)

Type: LD_0 [X]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [ ]

Species/strain: New Zealand albino rabbits – male and female

Value: > 2000 mg/kg.

Method: Modification of OECD Limit Test. A single dose (2000 mg/kg) was given dermally to 5 male and 5 female rabbits, allowed to stay on the skin for 24 hours, and the animals were then observed for 14 days post-dosing. Clinical signs and body weights were monitored periodically and gross autopsies were performed upon termination.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Undiluted NMA

Reliability: [2] valid with restrictions.

Remarks: All rabbits survived and gained weight through 14 days post-dosing. Clinical signs included slight nasal discharge and loss of appetite. Mild skin irritation was noted on several occasions. Necropsies were unremarkable.

Reference: Food and Drug Research Laboratories, Study No. 6771F, 3/21/81.

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

No Data

(2) NON-BACTERIAL *IN VITRO TEST* (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

(a)

Type of Test:	Primary Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderately irritating [ ]; Slightly irritating [X]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method:	Draize Test (Modification of OECD test)
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	On a scale of 8, a 50% suspension in PEG 400 was scored 0.75. No irritation was seen at a concentration of 6.5%
Reference:	FDRL Report of Study 6771-F, 3/5/82.

(b)

Type of Test:	Primary Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderately irritating [X]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method:	Draize Test (Modification of OECD Test)
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	Undiluted NMA was scored 3.9 on a scale of 8.
Reference:	FDRL Report of Study 6771-F, 3/5/82.

(2) EYE IRRITATION/CORROSION

(a)

Type of Test:	Acute Eye Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive **[X]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No wash. 83 on scale of 110 at 72 hours.
Reference:	FDRL Report of Study 6771-F, 2/27/81.

(b)

Type of Test:	Acute Eye Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[X]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	4 second washout. 12-37 on scale of 110 at 72 H.
Reference:	FDRL Report of Study 6771-F, 3/21/81

(c)

Type of Test:	Acute Eye Irritation
Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[X]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification:	Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No wash. 67 on scale of 110 at 72 H.
Reference:	Ferber, K.H./J.F. Best (letter), 10/10/66

B. SKIN SENSITIZATION

Type:	
Species/Strain:	Human
Results:	Sensitizing **[X]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification:	Sensitizing **[X]**; Not sensitizing **[ ]**
Method:	Sensitization Patch Test
Test Substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	Thirty four (34) out of 53 human subjects showed skin reactions during induction and at challenge indicating positive evidence of sensitization.
Reference:	FDRL, 5/7/82.

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were for NMA. By analogy to other acid anhydrides, NMA would be expected to cause respiratory sensitization. Industrial medical surveillance has indicated that NMA causes respiratory sensitization. Symptoms of over-exposure may include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

Type:	Industrial/Medical Surveillance
Results:	Source: Buffalo Color Corporation A number of customers have advised of complaints of asthmatic reactions to inhaled NMA. Manufacturers have less trouble in this regard probably because of better enclosure and ventilation. Transient eye and lung irritation have occasionally been reported.
Remarks:	Manufactured by Buffalo Color Corporation for a number of years without serious or lasting effects. No special medical surveillance to date. Personal and area monitoring data based on TOC of dust samples as of 1987 indicate compliance with BCC LV and CV with some exceptions. No epidemiology.
Reference:	Buffalo Color Corporation, 12/95

7. REFERENCES

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 6

APPLICABLE ROBUST SUMMARIES (SECTION 5)

FOR

PHTHALIC ANHYDRIDE (85-44-9)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

November, 2001

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5. TOXICITY

A. ACUTE TOXICITY –

Not used as supporting argument

B. REPEATED DOSE (General)

Type:	Two-year chronic toxicity / carcinogenicity study
Species/Strain:	Fischer 344 rats and B6C3F mice; 50 animals/sex/species for the test compound; 20 animals/sex/species for the control
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Oral feeding
Exposure Period:	102-105 weeks
Frequency of Treatment:	Daily
Post-Observation Period:	None
Dose:	0, 7500 and 15,000 ppm for 105 weeks for rats 25,000 and 50,000 ppm for 32 weeks for mice - subsequently reduced (due to weight loss) to: - 12,500 and 25,000 ppm for males for 72 additional weeks - 6,250 and 12,500 ppm for females for 72 additional weeks
Controls:	Concurrent Vehicle (Food alone)
Results:	Body weight gains in male rats and in both sexes of mice were reduced by phthalic anhydride, but survival in all of the treated groups was unaffected. Phthalic anhydride was not carcinogenic in either rats (≤50,000ppm in the diet) or in male (≤32,692 ppm average dose) or female (≤24,038ppm average dose) mice dosed over a period of 105 weeks (rats) and 104 (weeks), respectively.
Method:	In accordance with NTP/NCI standard chronic bioassay methodology as described in the subsequent reference and elsewhere[DHEW Publ.No.(NIH)79-1715]. Briefly, phthalic anhydride was incorporated into the feed of rats and mice for 105 (rats) and 104 (mice) weeks, respectively, beginning at 4-6 weeks of age. The initial doses were estimated to be the MTD and ½ MTD, based on preliminary repeated-dose studies.
GLP:	Yes [**X**]; No [ ]; ? [ ]
Test Substance:	Phthalic anhydride (approximately 98.8% pure)
Remarks:	In an NCI range-finding feeding study prior to this chronic bioassay, rats and mice were given phthalic anhydride at food doses ranging from 6200ppm to 50,000ppm for 7 weeks. Body weights were depressed at ≥25,000ppm in rats but mice showed no body weight effects even at 50,000 ppm. The lowest dose showing histopathology was 25,000ppm. At this dose, the livers of rats showed slight centrilobular cytoplasmic vacuolization (4 of 5 males). No histopathology was seen in the mice. Other repeated dose studies in the literature (oral and inhalation) were conducted in the USSR and deemed to be inadequate. One other limited study (H.Friebel et al., *Arch. Gewerbepathol. Gewerbehyg.* 14: 465-482, 1956) utilized increasing oral doses in rats starting at 20mg/kg and doubled weekly for 9 weeks when the dosage reached 890 mg/kg. The rats showed severe nephrosis with destruction of the tubular epithelium of the kidneys, as well as gastric ulceration.
Reliability:	[2] Valid with restrictions
Reference:	Kluwe, W. M., et al., 1982.

C. GENETIC TOXICITY *IN VITRO*

(1) BACTERIAL

Type:	Bacterial reverse point mutation assay (Ames test)
Species/Strain:	*Salmonella typhimurium* bacteria (strains TA 98, TA 100, TA 1535 and TA 1537)
Test System:	Pre-incubation modification of the standard plate incorporation method
Concentration:	5 doses in a range from 1 to 666 µg/plate
Metabolic Activation:	With [**X**] Without [**X**]
Result:	Not mutagenic
Cytotoxic Concentration:	>666 µg/plate
Precipitation:	No data
Genotoxic Effects:	Negative in all strains with or without metabolic activation (liver homogenates from Aroclor^{R} 1254-induced SD rats)
Method:	Standard Ames Test as cited in Mutat.Res. 31: 347-364, 1975 and Haworth, S., et al. Environ.Mutagen.5(1): 3-142, 1983.
GLP:	Yes[ ] No[ ] ?[X]
Test Substance:	99+% purity phthalic anhydride (Aldrich)
Remarks:	Concurrent solvent and positive controls were included in all experiments. Each test was run twice. Final doses were based on results of a preliminary range finding study on TA 100 (+/- S9). Negative results in this test are consistent with others reported elsewhere (Florin, I., et al. Toxicology 15(3): 219-232, 1980, for example).
Reliability:	[2] Valid with restrictions
Reference:	Zeiger, E., et al., 1985

(2) NON-BACTERIAL

Type:	Chromosome Aberration Assay
System of Testing:	Chinese Hamster Ovary (CHO) Cells
Concentrations:	6.0, 8.0 and 10.0 mM solutions
Metabolic Activation:	With [**X**]; Without [**X**]
Results:	With S9 activation, toxicity was apparent, precipitate was visible at 8 to 10 mM, and a small but non-significant increase in chromosome aberrations was seen at a 10 mM concentration. Without S9 at a 10mM concentration, precipitate was visible, toxicity was apparent and there was an 18.5% increase (compared to 3% in controls) in chromosome aberrations.
Method:	Similar to OECD (1997) guideline recommendations. Methodology detailed in subsequent reference. Briefly, test compounds were dissolved in DMSO or distilled water, added to CHO cell cultures, and the cultures were incubated for 3 hours at 37°C. Treatment was for 3 hours and aberrations were scored in cells harvested 20 hours from the beginning of treatment. Approximately 200 cells from each point were scored for aberrations on coded slides. Gaps were noted but not included in aberration totals.
GLP:	Yes[ ] No[ ] ?[X]
Test Substance:	Phthalic anhydride - purity not given but believed to be 99+%, (Aldrich).

	Remarks: The positive result in this study, without activation, can be compared to an earlier negative result by Galloway et al. (*Environ.Mol.Mutagen.* 10(10):1-175, 1987. The authors indicated the positive result from this study is probably due to the use of a shorter treatment period (3 hours), later harvest time (20 hours vs. 14 hours), and a higher dose level (10mM vs. 2.03 mM) which was very toxic and gave precipitate. in the presence and absence of liver preparations from phenobarbital/B-naphthoflavone treated male SD rats
Reliability:	[2] Valid with restrictions
Reference:	Hilliard, C. A., et al., 1998.

D. REPRODUCTIVE TOXICITY

Type of Study:	"Chronic" inhalation toxicity
Species/Strain:	Albino Rats (Outbred – no strain)
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	Inhalation
Exposure Period:	45 days
Frequency of Treatment:	24 hour continuous treatment (for duration of exposure period)
Post exp. Observation:	2 weeks
Dose:	0, 0.02 mg/m^3, 0.2 mg/m^3, and 1.0 mg/m^3
Control Group:	Air only
Method:	Six (6) male rats per dose were tested. Minimal details were given on atmosphere generation, analytic accuracy and methodology in general. All observations were made 2 weeks following continuous 45 day exposure.
Test Substance:	Pure (According to State Standard GOST 5869-51)
Results:	At 2 weeks post-exposure to concentrations of 1 mg/m^3, sperm motility was only one-half (40 min) that of the controls (82 min). At 0.2 mg/m^3, sperm motility was only slightly reduced (60 min). Reductions in the content of ascorbic acid and nucleic acids in the testes were also seen and paralleled the reduction in sperm motility at both 1.0 and 0.2 mg/m^3. For reproductive toxicity in male rats, the lowest effect level after "chronic" exposure was 0.2mg/m^3. The maximum no-effect level was 0.02mg/m^3 for all parameters.
GLP:	Yes[ ] No[X] ?[ ]
Remarks:	This USSR study is severely limited in technical and scientific detail. In addition, exposure for 24 hours/day for 45 straight days is not relevant to occupational exposure situations. This study appears to be the only study in which adverse effects on the testes have been noted. Similar effects have never been reported. No supporting studies have been located. Despite lack of technical detail and an exposure period, which has little correlation with occupational exposure, this study has been cited several times in the open literature as an indication of male reproductive toxic effects.
Reliability:	[3] Not valid
Reference:	Protsenko, E. I., 1970.

E. DEVELOPMENTAL TOXICITY/TERATOGENICITY

(1) Preferred Study (for Phthalic acid, hydrolysis product of phthalic anhydride)

Type of Study:	Developmental toxicity study
Species/Strain:	Wistar pregnant female rats
Route of Administration:	Oral feeding
Exposure Period:	On days 7-16 of gestation
Frequency of Treatment:	Food containing compound was available *ad libitum* for 24 hours/day on days 7-16 of gestation
Duration of Test:	10 days of dosing (days 7-16 of gestation) with final sacrifice on day 20 of gestation for subsequent examination of uteri and fetuses.
Doses:	0, 1021, 1763 and 2981 mg/kg bw; 11 rats/dose
Control Group:	Basal diet only *ad libitum*
Method:	As described in subsequent reference. Briefly, pregnant rats were fed phthalic acid at dietary concentration of 1.25% (1021 mg/kg bw), 2.5% (1763 mg/kg bw) and 5.0% (2981mg/kg bw) *ad libitum* on days 7-16 of gestation and subsequently sacrificed for evaluation on Day 20 of gestation for skeletal and internal malformations. Methodology was basically consistent with OECD guidelines.
Test Substance:	Phthalic Acid, 99.5% purity (Aldrich)
Results:	No deaths or clinical signs were seen in the dams at any dose. At 2.5% and 5% in the diet, food consumption and body-weights of the dams were depressed compared to controls during days 7-16 of dosing. However, body weight gains were higher than controls at this dose on days 16-20 of gestation. No evidence of maternal toxicity was seen at 1.25% in the diet . At sacrifice on Day 20, male fetuses (but not female) in the 5% group were significantly lighter in weight than controls. Skeletal and internal examinations of fetuses were unremarkable. However, at 5% in the diet, the degree of ossification indicated by the number of ossification centers of the caudal vertebrae was significantly lower than controls. In conclusion, maternal toxicity was seen at 2.5% and above and minor fetal effects only at 5% in the diet. Under the conditions of this study, phthalic acid does not pose a unique hazard to the developing fetus.
GLP:	Yes[ ] No[ ] ?[X]
Remarks:	A dietary dose of 5% phthalic acid in the diet is the maximum dose used in feeding studies (nutritional basis). Minimal adverse fetal effects were seen only at 5% in the diet but not at 2.5 or 1.25%. However, maternal toxicity was evident at dietary concentrations of 2.5% and above. Phthalic acid was not a developmental toxin even at a dietary dose that induced maternal toxicity.
Reliability:	[2] Valid with restrictions
Reference:	Ema, M., et al., 1997

(2) Supporting study

Type:	Developmental toxicity study
Species/Strain:	CD-1 pregnant female mice
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	Intraperitoneal injection
Exposure Period:	On days 8 through 10 of gestation. Female mice were dosed with phthalic anhydride on days 8, 9 and 10 of gestation and sacrificed on Day 18 of gestation for subsequent examination of uteri and fetuses.
Frequency of Treatment:	Once a day by i.p. injection
Post exp. Observation:	No Data
Dose:	Four dose groups, 10 pregnant mice/dose, doses up to 203 mg/kg
Control Group:	Concurrent Vehicle (0.5% w/v carboxymethyl cellulose solution)
Results:	The dose that produced 'teratogenic' effects in 5% of the fetuses was estimated to be 59mg/kg. The dose producing 'teratogenic' effects in 50% of the fetuses was 203 mg/kg. Defects included skeletal malformations and cleft palate. No NOEL was reported.
Method:	As described in subsequent reference. Briefly, mice were dosed intraperitoneally on days 8-10 of gestation, using at least 4 dose levels and 10 mice/dose. They were sacrificed at Day 18 of gestation and examined for "major" developmental effects. Some minor defects were not classified as malformations: undescended testes (not surprising as sacrifice was on day 18), extra lung lobe, skeletal variants, et al. This type of study was apparently a "screening" study with limited exposure. Only 10 dams/dose were used in this abbreviated protocol.
Test Substance:	Phthalic anhydride (> 98% purity)
GLP:	Yes[ ] No[ ] ?[X]
Remarks:	This study was apparently meant to be used as a screening study for comparison purposes. A Relative Teratogenic Index (RTI) was to be calculated from doses producing adult toxicity and doses associated with teratogenicity. Series of compounds could then be compared. The use of the preceding results, utilizing such a limited protocol, is questionable.
Reliability:	[2] Valid with restrictions
Reference:	Fabro, S., et al., 1982.

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